MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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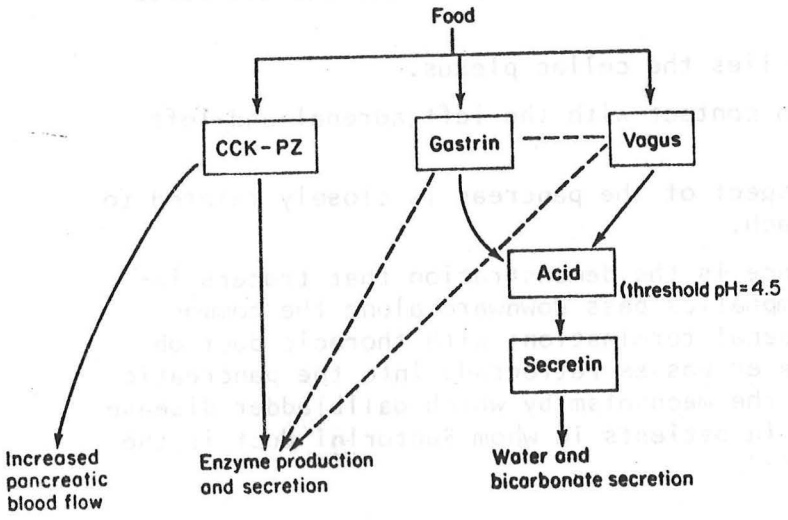
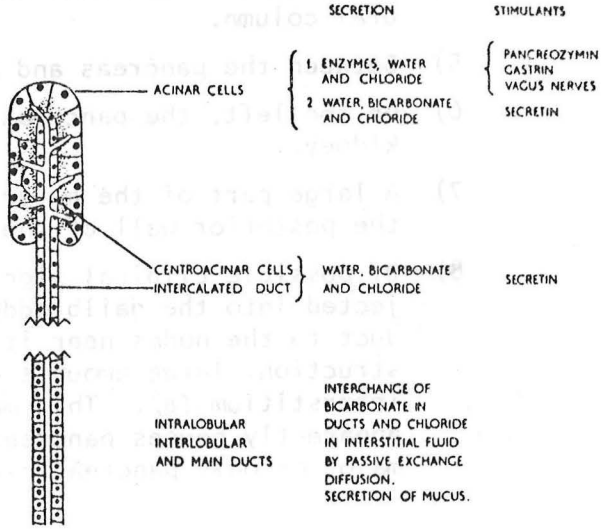
PANCREATITIS

CLINICALLY IMPORTANT ASPECTS OF PHYSIOLOGY

These are reviewed in Refs. 1-10. Fresh, uncontaminated pancreatic juice and extracts of pancreas have no proteolytic activity. The proteolytic enzymes and phospholipase A are secreted in an inactive form which are activated upon entering the duodenum by enterokinase, bile acids, etc. Pancreatic secretion contains a trypsin inhibitor, which is a polypeptide with a molecular weight of about 6000. This normally inactivates any trypsin formed from trypsinogen in the gland or duct system. However, its concentration in the juice or gland is much lower than that of trypsinogen, and it cannot prevent proteolytic activity of fully activated juice.

The mechanism of the pancreatic response to food is illustrated in the next two figures, with concepts taken mainly from Refs. 5 and 7. In addition to the mechanisms illustrated in the figures, distention of the stomach causes reflex stimulation of pancreatic enzyme secretion that can be blocked by vagotomy or splanchnic nerve section *(7)*.





Pancreozymin and secretin are released from duodenal and jejunal, but not ileal, mucosa in response to the presence of intraluminal products of digestion *(5)*. Most likely, the pancreas secretes at maximal rates after ingestion of normal food or in response to infusion of amino acids and emulsified fats in the duodenum *(5)*. The stimulatory effect of fatty acids depends on chain length; long-chain acids stimulate pancreatic secretion and medium-chain acids do not *(5)*. High concentrations of bile acids inhibit secretin and pancreozymin release *(39)* and glucagon inhibits the response of the pancreas to secretin and pancreozymin *(5)*. The proteolytic, lipolytic and amylolytic enzymes are secreted in parallel concentrations in man.

Increased metabolic requirements of the secreting pancreas require an increase in pancreatic blood flow *(7)*. There is evidence, as yet incomplete, that stimulation of the acinus cells by hormonal and neuronal agents also releases into the interstitial fluid nondigestive enzymes concerned with local production of vasodilator kinins *(7)*.

The exocrine pancreas has a tremendous reserve capacity, and the amount of digestive enzymes secreted in the duodenum far exceeds what is actually needed for normal digestion. Steatorrhea or creatorrhea does not result until the output of lipase or trypsin is 15% of normal or less. This explains the absence or late appearance of steatorrhea and creatorrhea in chronic pancreatitis and the lack of steatorrhea even after resection of 85% of the pancreas in some patients.

ANATOMICAL RELATIONS (2)

1) The tail of the pancreas lies in contact with the spleen.
2) The lower part of the common bile duct runs within the fibrous capsule of the pancreas, and in 90% of the cases also within the parenchyma of the pancreas.
3) The superior mesenteric vessels and portal vein lie directly behind the head of the pancreas.
4) The inferior vena cava and aorta lie between the pancreas and the vertebral column.
5) Between the pancreas and aorta lies the celiac plexus.
6) On the left, the pancreas is in contact with the left adrenal and left kidney.
7) A large part of the anterior aspect of the pancreas is closely related to the posterior wall of the stomach.
8) Of possible clinical significance is the demonstration that tracers injected into the gallbladder lymphatics pass downward along the common duct to the nodes near its duodenal termination; with thoracic duct obstruction, large amounts of tracer passes retrograde into the pancreatic interstitium *(8)*. This may be the mechanism by which gallbladder disease apparently causes pancreatitis in patients in whom Santorini duct is the major or only pancreatic duct *(21)*.

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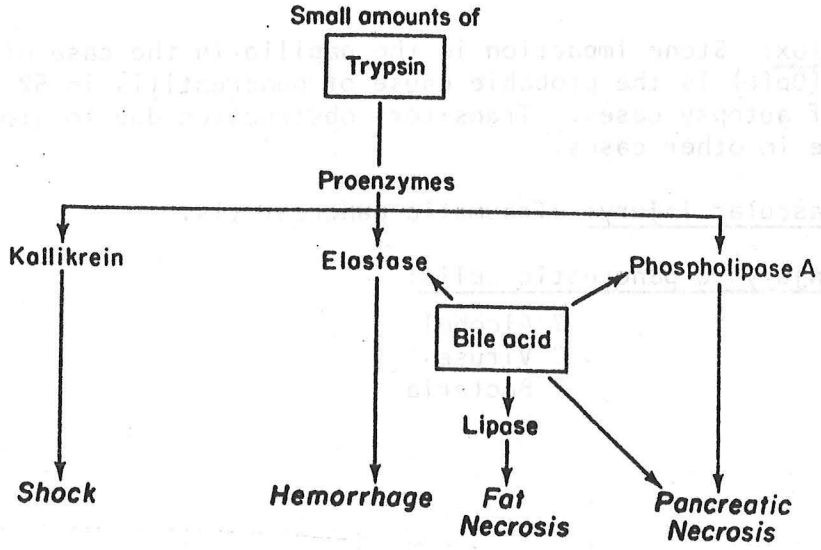
PATHOPHYSIOLOGY:

A. *Bacic Mechanism:* Assumed to be autodigestive. The precipitating factors in clinical disease remain a mystery.

B. *Current Hypothesis (11):*



C. *Activators and Effects of Pancreatic Enzymes (11):*

Characteristics of pancreatic enzymes and their effects on the pancreas*

	Activators	Inhibitors	Biochemical effect	Predominating histologic effect on pancreas
Trypsin	Enterokinase, autocatalytic kathepsin B (low pH!)	Kunitz inhibitor, Trasylol, serum inhibitors	Proteolysis, activation of proenzymes	Edema, liquefaction necrosis, hemorrhage
Chymotrypsin	Trypsin	Trasylol, serum inhibitors	Proteolysis	Edema, hemorrhage
Elastase	Trypsin	Serum inhibitors	Elastolysis	Hemorrhage
Kallikrein	Trypsin (low pH)	Trasylol, serum inhibitors	Kinin release	Edema
Phospholipase A	Trypsin (bile acids)		Formation of lysophosphatides	Coagulation necrosis, fat necrosis
Lipase	Bile acids		Splitting of triglycerides	Fat necrosis

*From Creutzfeldt W, Schmidt H: Aetiology and pathogenesis of pancreatitis (current concepts). Scand J Gastroenterol 5(Suppl 6):47-62, 1970.

D. *Some Likely Initiating Mechanisms (11):*

1) Reflux of duodenal contents: Probably the cause of pancreatitis in afferent loop obstruction, in cases of duodenal obstruction, and possibly after repeated vomiting, and in postoperative pancreatitis where sphincter atony is postulated.

2) Bile reflux: Stone impaction in the papilla in the case of a common channel (Opie) is the probable cause of pancreatitis in 5% of some series of autopsy cases. Transitory obstruction due to stone may be the cause in other cases.

3) Direct vascular injury: Traumatic pancreatitis.

4) Direct injury to pancreatic cells:

   ? Alcohol
   ? Viruses
   ? Bacteria

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PMH AUTOPSIES (January 1972-June 1974):

(Includes all cases where exocrine pancreatic disease was found and believed to be significant by the Pathology Department.)

1. 56 y/o man, chronic alcoholic, known hypertension, known diabetes for 3 years. Admitted with a 2-day history of abdominal pain and for 4 hours he had not urinated. He had a severe adynamic ileus and severe shock. 13 L of fluid were given in 18 hours to keep CVP above 5. Levophed was also used. The patient had lactic acid acidosis, a creatinine of 5, amylase 6400, WBC 15,000, and the serum was lipemic. He was afebrile and 2 blood cultures were sterile. He was treated with cleocin and gentamicin. He died on the second hospital day.

   Autopsy: Acute hemorrhagic pancreatic necrosis, fat necrosis. Gas gangrene liver and spleen. Ileus. K-W disease. Ischemic necrosis of the small bowel.

   Comment: Irreversible shock from hemorrhagic pancreatitis. Diabetes probably predisposed to clostridial gas gangrene.

2. 58 y/o WM, heavy drinker in the past. Admitted with abdominal pain and jaundice. Patient appeared "a little dehydrated" but was in no distress. BP 90/70 and vital signs were "stable" throughout his entire hospitalization, apparently being taken several times a day. Bilirubin 8, SGOT 3,000, Alk. Phos. 110 (N < 35), pro time 40 sec and did not correct with vitamin K. BUN 21, amylase normal on admission. Initial diagnosis was severe hepatitis. He was started on a low fat diet, was given glucose IV but no salt. Demerol was given for pain q2h. Two days later, after GI x-ray studies (including enemas and laxatives), the patient was noted to be oliguric and his creatinine was 6. The amylase was 361 and 380. He was transferred to PMH for dialysis and died 14 hours later.

   Autopsy: 1) Massive hemorrhagic pancreatitis, with complete destruction of the pancreas.
   2) Acute tubular necrosis
   3) Gangrene of distal small bowel and colon
   4) Centrilobular hemorrhagic necrosis of the liver
   (Nos. 2, 3 and 4 were all due to shock.)

   Comment: Shock not recognized or treated. Pancreatitis not recognized or treated. Severe pancreatitis can be present with normal serum amylase.

3. 47 y/o WM, heavy alcoholic, 2 previous admissions for pancreatitis. Admitted with RUQ abdominal pain, enlarged liver, jaundice and ascites. BP normal. Amylase < 320 on two occasions. Ca 8.2. Admitting diagnosis was gallbladder disease vs. alcoholic hepatitis. He was fed a low protein diet which he ate well initially according to the nurses' notes. He was given Talwin 3-4 x per day for pain. Paracentesis showed protein of 0.7, RBC 1,000, WBC 490 (70% polys). X-ray on admission showed dilated loops of small bowel consistent with adynamic ileus (this x-ray was seen by the house staff but not read by a radiologist until 10 days after it was taken and 8 days after the patient died). The patient died 2 days after admission without a suspicion that he might have pancreatitis.

   Autopsy: Acute hemorrhagic pancreatitis, fat necrosis, chronic pancreatitis. Portal cirrhosis.

Comment: Pancreatitis not recognized (normal amylase). He was given food and Talwin during his hospitalization. The x-ray showed an ileus and this would have suggested at least that the patient should not be fed.

4. 52 y/o WM, non-alchoholic, admitted with abdominal pain, abdominal distention and fever. BP 100/80 (but patient was known to have hypertension in the past). Initial impression was that he had a GI malignancy. A regular diet was ordered and demerol was given for pain. A barium enema and IVP were done the next day. Two days after admission upper GI and gallbladder x-rays were done, and these suggested a pancreatic mass pressing on the stomach. The amylase was elevated and therapy for pancreatitis was started about 2 days after admission. This included fluids, electrolytes, NG suction and keflin and kanamycin. An exploratory laparotomy was done and revealed pancreatitis, with no abscess or pseudocyst. Postoperatively he developed GI bleeding and renal failure and was transferred to PMH. He died 5 days later.

   Autopsy: Acute interstitial pancreatitis and pancreatic abscess (E. coli), peritonitis, bacteremia, intravascular coagulation, renal tubular necrosis, massive bleeding from the GI tract.

   Comment: Pancreatic abscess complicating interstitial pancreatitis. Delayed recognition and therapy for pancreatitis. Before dx made, patient had food, laxatives, enemas and demerol.

5. 41 y/o WM, alcoholic. Known hypertension and renal failure with creatinine of 10. On 6th hospital day he developed abdominal pain and severe epigastric tenderness. Amylase < 320 on admission, but rose to 427 when pain started. His amylase remained elevated to as high as 1600 (lipase 6.3) in spite of 6 days of NG suction. The NG tube was then removed and the patient fed. Although he had only moderate and inconstant pain, the amylase remained elevated. The patient died unexpectedly 30 days after admission.

   Autopsy: Acute interstitial and hemorrhagic pancreatitis, chronic pancreatitis with two small pseudocysts. Peripancreatic fat necrosis. Bronchopneumonia.

   Comment: Cause of chronic pancreatitis presumably alcohol. Acute pancreatitis may have been precipitated by uremia or drugs. This case illustrates the difficulty in managing patients whose pancreatitis does not resolve promptly after NG suction, especially when nutrition is poor to begin with.

6. 65 y/o WM. In 1970 he had laparotomy for pyloric channel ulcer. No ulcer was found, but a mass was felt in the head of the pancreas, and a radical Whipple procedure was done. The pancreas was histologically normal and even on step sections no cancer could be found. Postoperatively he developed severe malabsorption and malnutrition, dumping syndrome and finally hepatic disease and died in 1974.

   Autopsy: Stenosis of the hepatic duct at its anastomosis with the intestine, extensive fatty metamorphosis of the liver. The remaining pancreas was a fibrotic scar, and the pancreatic duct anastomosis to the intestine was completely occluded.

   Comment: Normal pancreas simulating a pancreatic cancer resulted in radical surgery which ultimately proved fatal to the patient.

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7. 43 y/o WM. Alcoholic. Recurrent pancreatitis with diabetes, pancreatic calcification, malabsorption, and pseudocyst. Surgical drainage in 1967. Died in 1973 after episodes of hypoglycemia. ? insulin overdosage.

   Autopsy: Bronchopneumonia. Fibrotic, scarred and calcified pancreas. A small pseudocyst was drained by Roux-En-Y.

   Comment: End-stage pancreatic fibrosis; pseudocyst successfully drained. Death probably caused by hypoglycemia. Marks and Bank *(20)* reported two patients with chronic pancreatitis who died of irreversible hypoglycemia and two others had severe insulin reaction repeatedly. They suggest that alcohol markedly reduced insulin requirements in these patients. See also Ref. 50.

8. 51 y/o BF. Abdominal pain, obstructive jaundice, weight loss, no abdominal mass, amylase 1068.

   Autopsy: Adenocarcinoma head of pancreas with invasion of duodenum, compression of portal vein, obstruction of the common bile duct and pancreatic duct, and metastasis to the liver and lymph nodes. The gallbladder and bile ducts were markedly dilated. Fibrotic atrophy of the body and tail of the pancreas, with acute and chronic pancreatitis and peripancreatic necrosis.

   Comment: Cancer obstructed the pancreatic duct and caused pancreatitis.

9. 43 y/o WM. Weakness, jaundice, pale stools and dark urine, and weight loss for 6 weeks. Shortly before admission he suddenly developed massive ascites. No abdominal pain. The patient was not an alcoholic. Amylase normal. LFT showed obstructive jaundice. He died shortly after exploratory laparotomy, which revealed widespread cancer.

   Autopsy: Showed cancer of the body and tail of the pancreas, which extended to obstruct the common bile duct. The head of the pancreas was free of tumor. There were two pseudocysts in the pancreas; one in the body measured 4 cm, one in the tail was 8 cm and compressed the stomach. The gallbladder and bile ducts were markedly dilated. There widespread metastases in mesentary, lymph nodes and liver.

   Comment: Painless obstructive jaundice due to cancer in the body and tail of the pancreas. Two pseudocysts. Amylase normal.

HOSPITAL ADMISSIONS TO PMH FOR PANCREATITIS IN 1972

One hundred seventy-two patients were admitted to PMH with some form of pancreatitis in 1972. Some were admitted more than once and there was a total of 194 admissions for pancreatitis in that year. All but 7 charts were found and reviewed by Martha Hicks, Barbara Bailey and the author.

The type and etiology of pancreatitis in these patients is shown in the next table:

ACUTE PANCREATITIS	No. Pts.	Male/Female	No. Adm.	No. Adm. Medical Service	Total No. Hospital Days	No. Deaths	No. Operated During Admission for Pancreatitis
Alcohol*	102	79/23	121	67	993	1	1
G.B. disease	12	3/9	14	1	150	0	3
Idiopathic	20	12/8	21	5	165	0	1
Cancer	3						
Narcotics	3						
Post-Op	3						
Trauma	14						
Hyperosmolar coma	1						
Hyperlipidemia	1						
CHRONIC PANCREATITIS							
Steatorrhea	5						
Diabetes	1						
CHARTS MISSING	-- 7						

*Four patients classified as having alcoholic pancreatitis also had gallbladder disease and 11 patients with alcoholic pancreatitis also had ulcer-like deformity by x-ray. Alcohol seemed the more likely etiology of pancreatitis in these patients. The one death occurred in the only patient who was hypotensive. Death in this case was due to cardiac arrest after the hypotension had been corrected by salt infusions. The operation in the patient with alcoholic pancreatitis was for drainage of a pseudocyst. The operation in the patient with idiopathic pancreatitis was an appendectomy which was done before it was realized the patient had pancreatitis. (The appendix was normal and the pain was presumably due to pancreatitis.)

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The patients with alcoholic, gallbladder-related, and idiopathic pancreatitis were subjected to further analysis, and the results are shown in the following tables:

AGE

	Alc.	G.B.	Idio.
< 20	0	2	1
20-30	11	4	10
30-40	40	3	4
40-50	29	0	1
50-60	16	1	3
> 60	6	2	1
Total	102	12	20

NO. DAYS IN HOSPITAL

	Alc.	G.B.	Idio.
< 1 week	69	3	10
1-2	36	8	8
2-3	12	1	3
> 3	6	2	0
Total	121	14	21

AMYLASE ON ADMISSION

	Alc.	G.B.	Idio.
< 320	9	0	3
> 320	109	14	18
Total	118	14	21

HIGHEST AMYLASE

	Alc.	G.B.	Idio.
< 320	5	0	0
320-400	20	3	8
401-600	28	0	5
600-1000	28	1	3
1000-2000	25	1	2
2-4000	10	7	3
> 4000	5	2	0
Total	121	14	21

In 60% of the patients the amylase was elevated for less than 3 days; in 83% it was elevated for less than 1 week; in 90% it was elevated for less than 2 weeks; in 10% it was still elevated on discharge from the hospital.

INITIAL DIASTOLIC BP

	Alc.	G.B.	Idio.
< 40	1	0	0
40-49	0	0	0
50-59	3	0	1
60-69	7	0	0
70-79	18	4	4
80-89	27	6	7
90-99	26	3	5
100-110	24	0	4
> 110	11	1	0
Total	117	14	21

FALL IN Hgb AFTER FLUIDS, ETC.

Hgb.	Alc.	G.B.	Idio.
0	26	4	6
0.0.9	20	2	3
1-1.9	28	3	11
2-2.9	21	3	0
3-3.9	7	2	1
4-4.9	7	0	0
> 5	9	0	0
Total	108	14	21

HIGHEST TOTAL BILIRUBIN

	Alc.	G.B.	Idio.
< 1	48	4	14
1-1.9	41	9	4
2.0-2.9	8	1	1
3-5	7	0	0
5-8	3	0	0
> 8	1	0	0
Total	108	14	19

CLINICAL MANIFESTATIONS ON ADM.

	Alc.	G.B.	Idio.
Pain	108	13	13
No pain	5	1	1
Vomiting	75	10	13
Seizures	9	0	0
DKA	2	0	0
Diarrhea	3	0	0

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HIGHEST WBC

	Alc.	G.B.	Idio.
< 6000	6	0	1
6-9000	32	4	7
9-12,000	42	3	3
12-15,000	20	1	6
15-18,000	13	4	3
18-21,000	2	0	1
21-25,000	2	1	0
25-30	0	1	0
30-40	0	0	0
Total	117	14	21

HIGHEST TEMPERATURE

	Alc.	G.B.	Idio.
< 99	7	0	0
99-99.9	25	3	5
100-100.9	49	4	8
101-101.9	23	1	5
102-103	12	4	2
> 103	3	1	1
Total	119	13	21

HIGHEST BUN

	Alc.	G.B.	Idio.
< 15	66	9	14
15-19	15	3	5
20-30	13	1	0
30-40	3	0	0
40-50	2	0	0
50-70	2	0	0
> 70	2	0	1
Total	103	13	20

HIGHEST CREATININE

	Alc.	G.B.	Idio.
< 1.5	82	9	14
1.5-2	2	0	0
2-3	2	0	0
3-4	4	0	0
4-6	3	0	1
6-8	2	0	0
> 8	1	0	0
Total	96	9	15

ADMITTING DIAGNOSIS

	Alc.	G.B.	Idio.
Pancreatitis	104	11	17
DKA	7	0	1
Seizure	1	0	0
Liver disease	1	0	0
GI bleed	1	0	0
PUD	1	0	0
GB disease	1	4	1
Other	4	0	2
Total	120	15	21

Complications in 156 Admissions for Alcohol, Gallbladder, and Idiopathic Acute Pancreatitis

Shock	1
Renal failure	1
Pseudocyst	2
Abdominal mass	3
Ileus	3
GI bleeding	11
Pulmonary	10
DKA	8
Lactic acidosis	1
Hyperlipemia	3
Hepatitis	8
Deaths	1

SERUM CALCIUM

	Alcoholic	Gallbladder	Idiopathic
> 9	78	10	13
8-9	17	3	2
7-8	5	1	0
< 7	1	0	0
Unknown	20	0	6

General Comments About PMH Patients: Patients with alcoholic pancreatitis had been drinking for 5 to 20 years. Attacks of pain tended to start on the afternoon after a bout of heavy drinking, as emphasized by Marks and Bank *(20)*. Vomiting was frequent, but it almost always started after the pain.

Pain tended to subside 1-3 days after starting treatment, which consisted of keeping the patients NPO, NG suction for 2-7 days, and IV fluids. Fluid therapy in

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the first 24 hours averaged 2990 ml of isotonic salt solution and 1060 ml 5% D/W. Twenty-seven per cent of the patients admitted to the Medical Service with alcoholic pancreatitis received antibiotics, compared to 73% admitted to the Surgical Service. All patients with gallbladder-associated and idiopathic pancreatitis received antibiotics. Tetracycline, kanamycin, chloromycetin, ampicillin, keflin and methicillin were used.

Fifty-four per cent of the patients were given narcotics for pain. Anticholinergic drugs were often used. None of the patients had an emergency laparotomy for a complication of pancreatitis.

Five patients had fever > 103. Two of these had atelectasis, lower lobe infiltrates and pleural effusions. Another had a urinary tract infection, possibly secondary to catheterization. In two, no cause for high fever other than pancreatitis was found.

Seven other patients had a WBC > 18,000. One had an LLL infiltrate or atelectasis, another had peritonitis after peritoneal dialysis, and one possibly had ascending cholangitis. One had SS disease and always had a high WBC. In three, no cause for the high WBC other than pancreatitis was found.

Some important topics and references that will not be discussed in detail:

1) An excellent controlled, double-blind study of Trasylol (proteolytic enzyme inhibitor) in the treatment of acute pancreatitis was reported by Trapnell et al. *(77)*. The patients had either gallstone or idiopathic pancreatitis (alcohol pancreatitis is practically non-existent in England). There was a mortality of 4 out of 53 cases (7.5%) in those treated with Trasylol and 13 out of 52 cases (25%) in the placebo group (P = .05).

2) The value of serum calcium in prognosis of acute pancreatitis: Reference 54 claims it to be of no value, while Feller et al. *(34)* found no mortality in 75 patients whose serum calcium was above 9 and 10 deaths in 45 patients if the serum calcium was less than 8. The serum calcium was not measured in the single patient who died in the 1972 PMH series. In the 4 patients in the autopsy series who died with acute hemorrhagic pancreatitis (Cases 1-4), the Ca was not measured in Case 1, was 7.2 (alb. 3.4) in Case 2, was 8.2 in Case 3, and was 7.1 in Case 4 (alb. 1.8). The mechanism of hypocalcemia is uncertain, with precipitation in areas of fat necrosis, glucagon release and low magnesium being postulated *(16)*.

3) Serum amylase and lipase, amylase clearance, etc.: See Refs. 78, 66 and 16.

4) Surgical intervention in acute necrotizing pancreatitis: (Refs. 76 and 79). Sometimes necessary to establish diagnosis or to treat the many possible complications of the disease. If the patient is dying of acute pancreatitis, as in some of our autopsy cases, a pancreatectomy might be considered, but it probably must be done early to do much good *(76)*.

5) Necessity of NG suction in treating mild alcoholic pancreatitis has recently been questioned *(80)* on the basis of a small (29 patients) study. However, the fact

that patients who received suction had less pain 1 and 2 days after therapy (P = .09 and .06) suggests that suction reduces pancreatic inflammation and that in more severe cases it might be important. Since one can't always tell on admission how severe the pancreatitis is going to be, NG suction should, in the author's opinion, be used routinely. Not only does it remove gastric juice which can stimulate pancreatic secretions, but it helps insure that the patient will not be given food. Most likely, omission of food is the most important factor in reducing pancreatic inflammation.

6) If sepsis in and around the pancreas is suspected, Dr. Sanford says that a combination of penicillin, gentamicin and clindomycin (or chloromycetin) would give broad coverage of the bacteria likely to be involved.

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REFERENCES FOR SOME UNUSUAL OR POORLY RECOGNIZED CAUSES OF PANCREATITIS

(A) *Drugs:*

Birth Control Pill:

Brit. Med. J. 4:551, 1972; Brit. Med. J. 4:688, 1973; Military Med. 136:578, 1971; NEJM 289:552, 1973; Metabolism 21:657, 1972

Thiazides:

Gastro. 62:695, 1972

Imuran:

Gastro. 62:1040, 1972

Steroids:

Am. J. Dis. Child. 125:726, 1973

Phenformin:

Ann. Int. Med.: 77:324, 1972; 78:306, 1973; 78:307, 1973

Diazoxide (in a patient with chronic renal failure):

Lancet 1:1397, 1972

(B) *Associated with Other Diseases and Conditions:*

Pregnancy: Check previous references on birth control pill.

Renal Transplantation: (23 cases out of 1,321 transplants)

Ann. Surg. 171:309, 1970

Bechet's

Ann. Int. Med. 75:561, 1971

Hyperlipidemia:

Am. J. Dig. Dis. 18:767, 1973; Am. J. Med. 54:161, 1973; Ann. Surg. 177:483, 1973; NEJM 289:586, 1973; J. Roy. Coll. Surg. Edinb. 18:120, 1973; Am. J. Med. 56:482, 1974; Trans. Assoc. Am. Phy. 86:245, 1973; JAMA 225:1331, 1973 (suppression of amylase by lipids).

Acute and Fulminant Hepatic Failure:

Gut 14:428, 1973; John Hopkins Med. J. 133:156, 1973; Am. J. Dig. Dis. 18: 1079, 1973

Hyperparathyroidism - Hyper and Normocalcemic:

J. Pediatrics 83:275, 1973; Cleveland Clin. Quart. 41:39, 1974

Thrombolic Thrombocytopenic Purpura:

Am. J. Dig. Dis. 18:238, 1973

Hyperosmolar Coma:

N. Y. State J. Med. 72:1741, 1972

Lactic Acid Acidosis:

N. Y. State J. Med. 72:1741, 1972

Cystic Fibrosis:

Pediatrics 51:49, 1973

Hypothermia: (accidental and myxedema)

Brit. Med. J. 1:245, 1974; Brit. Med.J. 2:58, 1974; Brit. Med. J. 1:159, 1974; Brit. Med. J. 4:757, 1973

Calcium Infusion in a Dialysis Patient:

Arch. Surg. 108:218, 1974

Hypercalcemia During IV Hyperalimentation:

Arch. Surg. 108:213, 1974

(C) *Intra-abdominal Disorders and Injuries*:

Choledochal Cyst and Fusiform Dilatation of the Common Bile Duct:

Pediatrics 51:289, 1973; J. Pediatric Surg. 8:907, 1973

Trauma and Postoperative Injury:

Ann. Surg. 147:263, 1957

Cancer of Pancreas: (Primary or Secondary)

Mayo Clin. Proc. 46:174, 1971; Am. J. Gastro. 60:290, 1973

Peroral Cholangiopancreatography:

Gastro. 64:320, 1973; Gastrointestinal Endoscopy 20:28, 1973; Gut 14: 431, 1973; Gastro. Endoscopy 20:56, 1973; Gastro. Endoscopy 20:170, 1974

Stenosis of Sphincter of Oddi and Papillitis:

Surg. Cl. No. Amer. 53:1149, 1973

Regional Enteritis:

Gastro. 63:713, 1972

Duodenal Diverticulum:

Am. J. Gastro. 60:273, 1973

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Gallstones, Gallstone Migration, etc.:

NEJM 290:484, 1974; NEJM 290:1201, 1974; Gut 13:996, 1972

(D) *Infections:*

Mycoplasma pneumoniae:

Brit. M. J.: 2:240, 1973; 2:554, 1973

Rubella:

J. Pediatrics 80:465, 1972

Viral Hepatitis:

Calif. Med. 117:1, 1972 (Sept.). (Halothane hepatitis 2/33 had hepatitis; 7/16 with viral hepatitis had acute pancreatitis.) See also references on Acute and Fulminant Hepatic Failure.

Mumps (With and Without Paratitis):

Brit. Med. J. 1:529, 1973

Coxsackie B:

Brit. Med. J. 3:524, 1973

(E) *Hereditary (Some associated with amino-aciduria):*

Pediatrics 51:55, 1973; Scand. J. Gastro. 8:217, 1973; Arch. Surg. 108: 63, 1974; Am. J. Surg. 127:511, 1974

REFERENCES FOR SOME COMPLICATIONS OF PANCREATITIS

(A) *Abdominal:*

Severe Hemorrhage:

Am. J. Surg. 127:377, 1974; Lancet 1:847, 1972

Mass, Phlegmon and Abscess:

Arch. Surg. 108:545, 1974; Surg. Clin. No. Amer. 54:621, 1974; Med. J. Aust. 1:1241, 1973

Ischemic Bowel Necrosis:

Gastro. 58:709, 1970

Intestinal Obstruction:

Am. J. Dig. Dis. 19:179, 1974

Colon Perforation:

Dis. Colon and Rectum 17:106, 1974

Colon Necrosis, Fistula, etc.:

Ann. Surg. 179:403, 1974; Scand. J. Gastro. 7:375, 1972; Arch Surg. 104:708, 1972; Can. J. Surg. 16:393, 1973

Portal Hypertension and Portal Vein Thrombosis:

Am. J. Med. 52:228, 1972; Ann. Int. Med. 75:903, 1971

Ascites: (High protein, chylous, etc.)

S. African J. Surg. 10:235, 1972; African Med. J. 47:575, 1973; So. Med. J. 65:1377, 1972

Others for which a good reference could not be found: necrosis of spleen, A-V fistula, retroperitoneal fat necrosis with ureteral obstruction.

(B) *Systemic:*

Acute Respiratory Distress and Other Pulmonary Complications:

Am. J. Surg. 127:314, 1974; Ann. Int. Med. 78:789, 1973; Ann. Int. Med. 77:923, 1972; Ann. Int. Med. 78:788, 1973; Ann. Surg. 178:75, 1973; Br. Med. J. 4:610, 1972; Am. Rev. Resp. Dis.:106:97, 1972; So. Med. J. 66: 1016, 1973

Transient Hypertension:

SGO 138:235, 1974

DIC and Defibrination:

Ann. Int. Med. 76:73, 1972; Am. J. Surg. 105:714, 1963; Surgery 69:663, 1971

Renal Failure:

Brit. Med. J. 4:359, 1972; Brit. Med. J. 3:801, 1972; Int. Urology & Nephrol. 4:83, 1972

Pancytopenia:

Lancet 2:1363, 1972

Peripheral Fat Necrosis:

Med. Annals D.C. 42:319, 1973; Radiology 106:85, 1973

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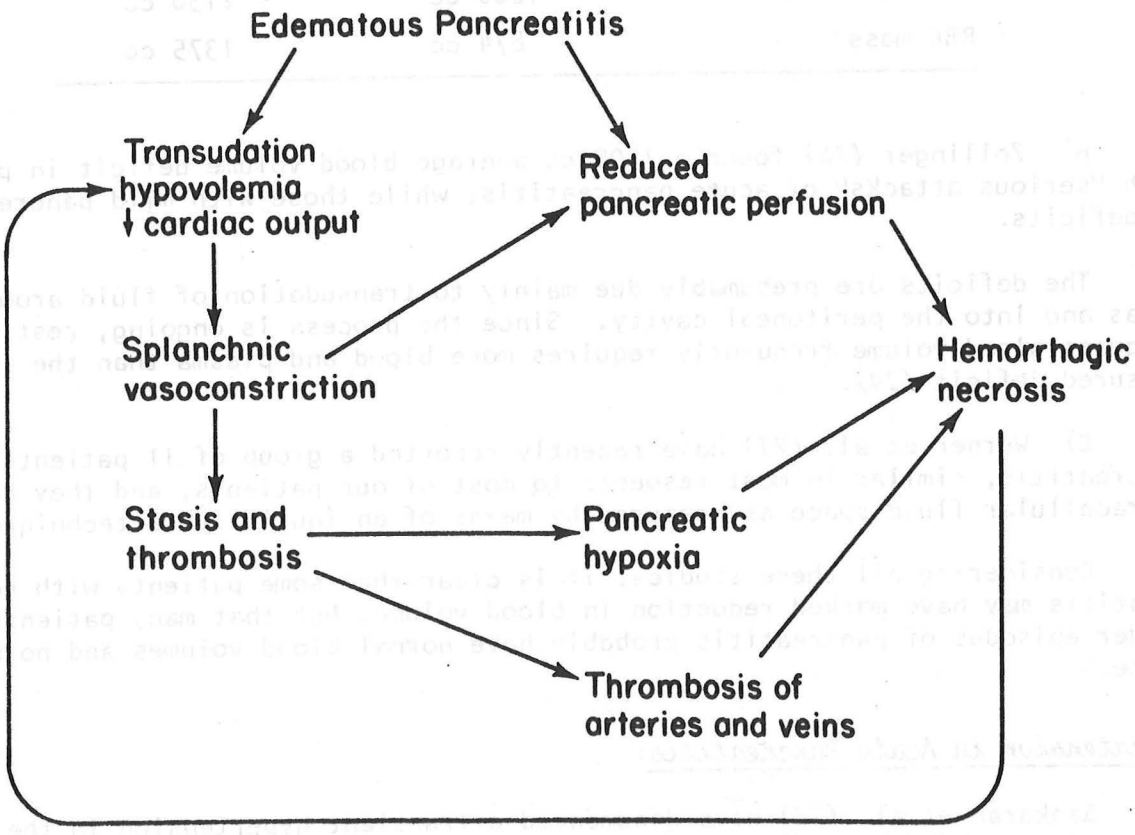
HEMODYNAMIC PROBLEMS IN ACUTE PANCREATITIS

PMH Series: Only one patient in the 1972 survey had an admission diastolic BP less than 50 (this is the only patient in our series who died), and diastolic pressures greater than 90 were present in about half the patients. Two patients in the PMH autopsy series died with shock, and one of these had acute tubular necrosis, and both had ischemic necrosis of the bowel.

Pancreatic and Splanchnic Blood Flow in Acute Pancreatitis: Pancreatic blood flow is reduced 40 to 60% in experimental acute pancreatitis. This is only partly explained by shock and reduction of cardiac output, since simultaneous measurement of blood flow in different splanchnic organs demonstrate that blood flow and perfusion are disproportionately reduced to the pancreas (67). Reduced pancreatic blood flow and pancreatic ischemia may be one major factor in converting edematous pancreatitis to hemorrhagic pancreatic necrosis. According to this thesis, hemodynamic changes are not only a manifestation of pancreatitis but also a cause of hemorrhagic necrosis. The marked splanchnic vasoconstriction accounts for ischemic changes in the gut.



In experimental pancreatitis, low molecular weight dextran infusions will prevent the progression of edematous to hemorrhagic pancreatitis *(12)*. These dextrans are better in this regard than saline, regular dextran or plasma. The low molecular weight dextrans are postulated to have the following actions:

a) Improved blood flow by a specific RBC disaggravating effect
b) ↑ plasma volume
c) Antithrombotic effect

Low molecular weight dextran might be useful in selected patients (those with shock, reduced urine flow, etc.), although clinical trials are limited *(13)*.

Blood Volume Measurements in Acute Pancreatitis:

A) Keith and Waltman *(14)* found the following blood volume deficits in patients with acute pancreatitis:

	Mean Deficit	Maximum Deficit
Whole blood volume	1806 cc	2510 cc
Plasma volume	1260 cc	2136 cc
RBC mass	874 cc	1375 cc

B) Zollinger *(15)* found a 1500 cc average blood volume deficit in patients with "serious attacks" of acute pancreatitis, while those with mild pancreatitis had no deficits.

The deficits are presumably due mainly to transudation of fluid around the pancreas and into the peritoneal cavity. Since the process is ongoing, restitution of adequate blood volume frequently requires more blood and plasma than the initially measured deficit *(14)*.

C) Werner et al. *(71)* have recently reported a group of 11 patients with acute pancreatitis, similar in most respects to most of our patients, and they had normal extracellular fluid space as measured by means of an inulin space technique.

Considering all these studies, it is clear that some patients with severe pancreatitis may have marked reduction in blood volume, but that many patients with milder episodes of pancreatitis probably have normal blood volumes and normal ECF space.

Hypertension in Acute Pancreatitis:

Sankaran et al. *(73)* have documented a transient hypertension in the acute phase of pancreatitis in 40 of 42 patients monitored prospectively. This hypertension was not seen in patients with other abdominal crises. Werner et al. *(71)* found hypertension in all 11 of their patients during acute pancreatitis, compared to blood

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pressure readings in the convalescent period. This was not due to fluid overload induced by IV solutions, since ECF space was normal.

Renal Hemodynamic Changes in Mild-to-Moderate Acute Pancreatitis:

Werner et al. made the following observations in 11 patients with acute pancreatitis (10 of their patients survived and one died of hemorrhagic pancreatitis).

	Acute Phase	Convalescence
GFR	89	96
Effective renal plasma flow (ml/min)	382	474
Renal vascular resistance (dyne-sec/cm^5)	11,006	7,814
Cardiac index (L/min/1.73 ml)	2.8	2.9
Total peripheral resistance (dyne-sec/cm^5)	2,030	1,433

The combination of an elevation of mean arterial blood pressure, elevated total peripheral resistance, increased renal vascular resistance in association with normal extracellular space suggests that a pressor substance may be released in acute pancreatitis, which has both systemic and renal effects. Renal vein renin was not increased in these patients. Regardless of the etiology, some factor causes an increase in both renal vascular resistance and total peripheral resistance during the acute phase of pancreatitis.

It should be emphasized that these studies were done in patients with the usual mild-to-moderate attacks of pancreatitis, and they wouldn't apply to patients in shock.

Renal Failure in Acute Pancreatitis:

Patients with acute pancreatitis who develop uremia have a mortality rate of 80% and if the uremia is severe enough to require dialysis, the mortality rate is 90 to 100% *(70)*. The presence of "oliguria" and "acute renal failure" also means a poor prognosis *(72, 68)*. Gordon et al. reported that 6 of 41 patients with acute pancreatitis had acute renal failure, which they defined as a BUN greater than 100, which was not corrected by simple fluid replacement. Three of their 6 patients died *(68)*. Careful scrutiny of these patients' charts and records failed to reveal any appreciable changes in blood pressures preceding most cases of acute renal failure. They postulate that vasoactive substances may disturb regulatory mechanisms of the renal circulation. Note that in our autopsy case No. 2, severe shock was present, but that his vital signs were consistently normal. In the PMH hospital series, one patient had severe acute renal failure, required dialysis, and survived.

Although the cause of renal failure in acute pancreatitis is usually considered to be hypovolemia and ischemia, the functional aberrations in the kidney usually persist despite improvement in fluid and electrolyte therapy, and usually it is impossible to document episodes of "shock". It seems likely, however, that most of these patients are hypovolemic - see above data on blood volume measurements in patients with severe acute pancreatitis. Another possible cause of shock and hypotension in pancreatitis is the systemic release of kallikrein *(16)*.

Fluid Replacement in Patients with Acute Pancreatitis:

Many authors recommend the routine use of plasma, whole blood or dextran for the treatment of acute pancreatitis. Zollinger, for example, recommends two units of plasma for one unit of whole blood plus Ringer's lactate, apparently in all cases of acute pancreatitis *(15)*. The very low mortality rate in the PMH series, where only saline was used, suggests that these other volume expanders are not routinely necessary. However, if the patient has evidence of shock, reduced urine output (< 30 cc per hr), or elevated BUN or creatinine that does not correct promptly with salt infusions, whole blood, plasma or dextran should be used. A CVP should be inserted in such patients to monitor volume replacement. Urine output and BP tilt should be carefully observed in all patients with acute pancreatitis. Normal blood pressure is not good evidence against the presence of shock.

Vasopressors in Acute Pancreatitis with Shock:

Considering the theoretic importance of pancreatic vascular perfusion, the severe and disproportionate restriction of splanchnic blood flow in hypotensive and hypovolemic states *(42)*, and the fact that Levophed markedly constricts mesenteric and renal blood flow *(65)*, the use of Levophed (as used in autopsy case No. 1) may have detrimental rather than beneficial effects on the ultimate outcome of these patients. No clinical or experimental studies on this problem were found in the literature.

Although vasopressin reduces pancreatic blood flow in the normal animal, vasopressin elevates blood flow and perfusion in acute hemorrhagic pancreatitis, and reduces mortality in these animals. The author cautions against extrapolating the results in dogs to humans with acute pancreatitis *(67)*.

General Summary:

Hypotension, shock, oliguria or renal failure in patients with acute pancreatitis indicate a very high mortality rate, and normal vital signs are no assurance against the presence of severe shock that can kill the patient. Judging from our 1972 PMH survey, problems will be rare, but we should look carefully for them in every patient with acute pancreatitis.

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PROLONGED AND COMPLICATED ACUTE PANCREATITIS

As illustrated by Autopsy Case No. 5, prolonged and complicated acute pancreatitis carries a poor prognosis. Some clinical examples that fit into this category of prolonged and complicated pancreatitis are:

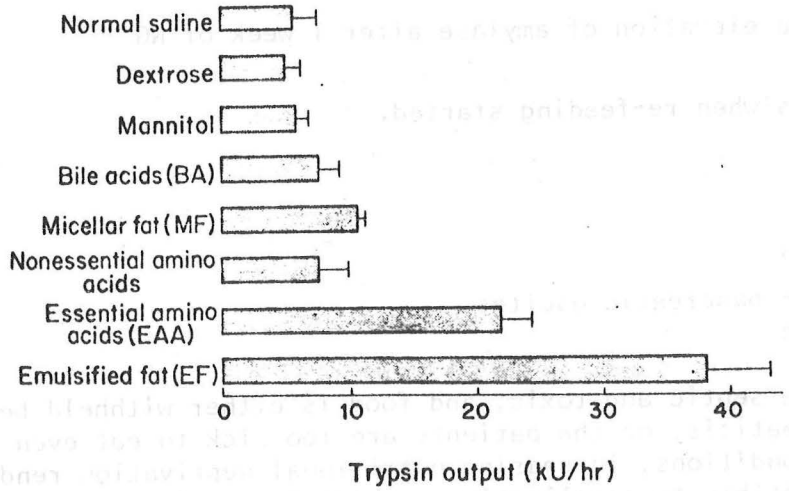
1. Continuing pain and elevation of amylase after 1 week of NG suction
2. Pancreatitis recurs when re-feeding started.
3. Pseudocysts
4. Pancreatic abscess
5. Pancreatic fistulas
    a) Spontaneous - pancreatic ascites
    b) Postoperative

Many of these patients are septic and toxic, and food is either withheld because it causes recurrent pancreatitis, or the patients are too sick to eat even if food is offered. Under these conditions, increasing nutritional deprivation renders the patient more and more susceptible to complications, which the patient is poorly equipped to handle. An incredibly rapid depletion of fat and protein stores occurs which must "be recorded to be believed" *(34)*. IV hyperalimentation can be used to advantage in some of these patients, but in most hospitals this therapy is impractical, and sepsis contradicts its use in many patients with prolonged and complicated acute pancreatitis.

Recently several authors *(33-37)* have recommended the use of an elemental diet in such patients. Although this seems incompatible with the general principle of pancreatic rest for acute pancreatitis, these workers claim that elemental diets stimulate less gastric acid and less pancreatic enzyme secretion than normal food. The rationale offered to explain this is that amino acids are less potent than polypeptides and protein in stimulating gastric acid and pancreatic secretion, that the elemental diets are <u>infused</u> into the stomach (bypassing the cephalic phase of secretion) or into the small bowel via per nasal tube or jejunostomy (bypassing both the cephalic and gastrin phases of gastric and pancreatic secretion). Intrajejunal infusion of <u>neutral</u> solutions would not stimulate acid secretion, gastrin or secretin release, and amino acids are, as noted previously, less potent releasers of pancreozymin than protein and polypeptides. Furthermore, infusing the diet into the jejunum would prevent gastric distention and thus avoid the reflex stimulation of pancreatic secretion which occurs when the gastric fundus or antrum is distended *(7)*. An obvious theoretical advantage of elemental diets over jejunal infusion of standard tube feeding mixture is that the former require no pancreatic enzymes for digestion, whereas standard tube feeding mixtures could not be absorbed unless the pancreas secreted its digestive enzymes.

Experiments to prove that elemental diets infused into the stomach or jejunum do, in fact, elicit less gastric and pancreatic secretion than normal food have all been done in dogs rather than humans, and even the animal experiments are not convincing. Furthermore, Go and co-workers *(38, 39)* have shown that normal humans

have near maximal pancreatic enzyme secretion in reponse to essential amino acids and emulsified fats that are infused into the duodenum. (Nonessential amino acids do not stimulate pancreatic enzyme secretion, and of the essential amino acids only phenylalanine, methionine, valine and tryptophan cause secretion.) All of these test solutions were adjusted to pH 6.3 or 6.0, so they are near the "neutral" pH recommended for elemental diet infusion. Further studies have shown that pancreatic enzyme secretion is stimulated equally (and near maximally) when amino acid mixtures are infused into the duodenum and jejunum, but not into the ileum *(40)*.



Nevertheless, at least 8 cases have been reported where elemental diets have been infused into either the stomach or proximal small intestine in patients with prolonged and complicated acute pancreatitis, apparently with great success *(33-35)*. Many of these patients were septic and IV hyperalimentation could not be used. In others, the 2 modes of alimentation were used sequentially. The authors claim that in each instance the patients were able to tolerate the elemental diets, and in several of the patients regular food was said to have produced an excerebration of pancreatitis. The patients showed subjective improvement, weight gain, fistula closure, etc., and all but one of the patients survived. An adequate nitrogen and caloric intake in excess of 1 gm of protein and 45 Kcal per kg weight was achieved in all cases. Balance studies showed that the patients reverted to positive nitrogen balance. The authors are so impressed with the problem of negative nitrogen balance that they believe some form of feeding (IV hyperalimentation and then elemental diet) should be started within 48 hours in all patients with severe pancreatitis *(34)*. Practical suggestions for the use of elemental diet infusions are given in Refs. 35 and 52. Slow and continuous infusion by a pump is mandatory.

Further work is needed to evaluate the benefits and hazards of elemental diets in patients with prolonged and complicated acute pancreatitis. For the present, it would be worth trying infusion of these diets in patients whenever the hazard of continuing negative nitrogen balance seems to outweigh the danger of aggravating a continuing pancreatitis.

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Another possible method of treating prolonged and complicated acute pancreatitis, with or without an elemental diet, is glucagon infusion *(74, 75)*. Glucagon suppresses exocrine pancreatic secretion, and Condon et al. *(75)* have treated 30 patients with glucagon infusion. One mg was given intravenously as an initial dose and this was followed by IV infusion of glucagon (1 to 1.5 mg q4h for 24-96 hr) in either 5% DW or NS. [This dose should markedly suppress pancreatic secretion according to the data of Go et al. *(5)*]. Ten of their patients were classifed as having severe pancreatitis. There were 2 deaths in this series (7%). Glucagon therapy was associated with relief of pain and clinical improvement in all patients, including the two who later died. Admittedly, the study was not controlled.

Still another drastic measure to consider in patients who appear to be dying of acute pancreatitis is near total pancreatectomy. Norton and Eiseman *(76)* have treated 4 patients with this procedure, and 3 of them lived. The operation is mainly recommended within the first 48 hours of admission.

CHRONIC RELAPSING PANCREATITIS

Case Report:

E.W. (379018): 44 y/o M: Chronic alcoholic with multiple admissions for pancreatitis characterized by abdominal pain, vomiting, and elevated amylase. These attacks responded to NG suction and IV fluids. On two admissions to the hospital he had alcoholic withdrawal symptoms, in spite of the fact that he claimed to have stopped drinking 6-12 months earlier.

His visits to PMH are summarized below:

April 1970 February 1970 December 1972 March 1973 June 1973	Admitted to hospital with pain and high amylase. He spent a total of 65 days in the hospital during these hospitalizations (8-20 days each).
February 13, 1974 February 19, 1974 March 23, 1974 July 23, 1974	Seen in EOR with abdominal pain and vomiting, but with normal amylase. Sent home.

He claims to have had no alcohol since 1973. An upper GI in 1973 suggested a pseudocyst (pressure defect on stomach), but a repeat study on 2-21-74 was normal. Two gallbladder x-rays were negative. He has severe calcification of the pancreas, but no malabsorption or diabetes.

On March 29, 1974, he was seen in Clinic and started on Talwin for chronic abdominal pain. He takes Talwin and/or codeine several times daily, and these prescriptions have been refilled on each of his subsequent Emergency Room and Clinic visits.

Etiology:

Alcohol is the major cause of chronic pancreatitis and accounts for about 75% of cases in the U.S. Biliary tract disease, hereditary pancreatitis, hyperlipidemia, and hypercalcemia are less common causes *(17-20)*. About 10 to 25% of the cases have no demonstrable etiology.

Some Generalizations About Chronic Alcoholic Pancreatitis:

1) It takes heavy drinking for 5 to 15 years to get alcoholic pancreatitis. (To get clinically evident cirrhosis of the liver, 10 to 25 years of drinking is usually required.) Temperate and occasional binge drinkers do not get pancreatitis.

2) When clinical manifestations first begin, the patient already has severe and chronic pathological changes in the pancreas.

3) Although pain is the major manifestation, severe complications can occur without pain.

Complications:

(A) Gambill et al. *(17)*, 20-year followup in 53 patients with chronic relapsing pancreatitis: The average age at onset of the disease was about 40. Almost all received surgery in an effort to control abdominal pain, directed mainly at the gall-

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bladder and sphincter and drainage of pseudocysts; none had pancreatectomy or pancreatic duct drainage. Twenty years after they were first seen, 33 were dead and 17 were known to be alive at an average age of 62. Ten of the 33 deaths were directly due to complications of pancreatitis.

Complications in 56 Patients

Complication		Duration of Pain Before Discovery of Complication
Diabetes	54%	9 years (1-22)
Steatorrhea	43%	8 years (0-24)
Pancreatic calcification	39%	9 years (1-22)
Pseudocyst	16%	
Abdominal abscess	13%	
Ascites	11%	
Abdominal vascular thrombosis	9%	

(B) *Complications in 113 Patients Studied by Levrat* (18)*

Transient jaundice	19%
GI hemorrhage	11%
Diabetes	22%
Steatorrhea	28%
Deaths	5%

* Followup was from less than 4 to greater than 20 years. Diabetes and steatorrhea occurred twice as frequently in the patients who had pancreatic calcification.

(C) *Marks and Bank*(20) - 148 Patients with Alcoholic Pancreatitis*

Diabetes	29
Steatorrhea	17
Cyst	21
Bleeding	12
Cirrhosis	17
Cancer pancreas	2

* See Ref. 50 for an update on their patients.

In those with calcific pancreatitis, diabetes was present in 60% and steatorrhea in 40%. Overt steatorrhea was almost always associated with diabetes, but not vice versa.

(D) *Other Complications of Chronic Pancreatitis*

1) Peptic ulcer up to 20% in some series (19)
2) Opiate addiction (23)
3) B_{12} malabsorption (19)
4) Pancreatic ascites (28, 29)

Genesis of Pain in Chronic Pancreatitis: Three Theories (27):

1) Kinking and distention of the pancreatic ductal system secondary to intraductal calculi and ductal stricture.
2) Peripancreatic inflammation.
3) Inflammation and scarring around nerves and nerve endings within the substance of the pancreas.

Pain and Narcotic Addiction: Three Opinions:

1) *Soergel (30):*

"Unrelieved pain drives a number of patients to suicide, causes decreased food intake with rapid weight loss even in the absence of steatorrhea, and leads the alcoholic back to the bottle. Although long-term use of narcotics has, indeed, caused some patients to become addicted, this risk appears small compared to the damage and suffering from persistent pain. Opiates, especially morphine, are not recommended in the treatment of acute pancreatitis because they cause spasm of the sphincter of Oddi, but there exists no specific contraindication to their use in chronic pancreatitis except, perhaps, in patients with the idiopathic form, some of whom may have stenosis of the sphincter of Oddi."

2) *Benson (31):*

"The danger of addiction is great, so narcotics should be avoided as much as possible. Aspirin should be given first for pain. All narcotics increase intraductal pressure, especially after meals."

3) *Frey (27):*

"Failure of medical therapy to relieve the pain of pancreatitis justifies surgical intervention. Attempts to alleviate the pain of pancreatitis over long intervals of time by reliance on narcotics are misguided and may result in addiction. Avoidance of narcotic addiction deserves a high priority among the indications for operation in chronic pancreatitis. Once narcotic addiction occurs, the opportunity to rehabilitate patients, even if later relieved of pancreatic pain, is markedly diminished."

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Natural History of Pain in Chronic Pancreatitis:

Gambill *(17)* reported that 13 of 17 patients known to be alive 20 years after the diagnosis of chronic relapsing pancreatitis were pain-free for an average of 16 years. The pain had disappeared after one or more operations directed mainly at the biliary tract, but in many instances the pain had gone away only several years after the last surgical procedure.

	No.*	Degree of Pain Relief		
		Complete	Partial	None
Alcoholics	15	6	5	4
Nonalcoholics	33	12	15	6

*Some of these patients died of pancreatic disease or from unrelated causes after the pain had disappeared.

Levrat et al. *(18)* studied 113 cases of chronic pancreatitis. The spontaneous course of the disease (without surgery) was followed for less than 4 years in 34 patients, for 5-9 years in 38, for 10-20 years in 20 patients, and for greater than 20 years in 11. Alcohol was an etiologic factor in 67 of their patients. Spontaneous relief of pain was observed in 46 cases (42%) and was complete in 36. The pain relief tended to occur about 8 years after the first symptom. The pain stabilized in 35 patients and continued or became worse in 32 others. Thirty-eight of the patients who continued to have pain were later operated on.

Thus, it appears that about 40% of patients will have a spontaneous remission of pain, usually about 8 years after the initial attack.

Effect of Alcohol Withdrawal:

Most workers agree that cessation of alcohol ingestion will usually prevent relapsing attacks of pain and relieve chronic pain, as well as the potentially fatal complications of pancreatitis *(19,20,23)*. Indeed, alcohol withdrawal is the only known worthwhile measure for preventing attacks of pancreatitis. If pain persists for long after alcohol is stopped, one should suspect a pseudocyst *(20)*. If it recurs several years after alcohol withdrawal, pancreatic cancer may have supervened.

Although pain is usually relieved by abstinence from alcohol, diabetes and steatorrhea may still develop at a later date *(19)*.

Surgical Treatment for Chronic Pancreatitis:

In evaluating the effects of surgery, one must keep in mind that spontaneous relief of pain occurs in about 40% of patients simply with the passage of time *(18)*, that cessation of alcohol will relieve pain in many patients *(19)*, and that surgical treatment may relieve pain by virtue of a placebo effect in about 30% of cases *(32)*. Some workers think that abstinence from alcohol is a prerequisite for a "good result from surgery" *(20)*, but others do not agree.

A. *In Idiopathic Pancreatitis:*

White recommends operating on all patients admitted to the hospital two times with pancreatitis if the etiology is doubtful *(21)*. This seems reasonable because a number of these patients will have gallstones that were undetected by x-ray. For example, of 36 patients operated on by White that were found to have biliary calculi, 8 had had no gallstones demonstrated on repeated x-rays of the gallbladder. A negative laparotomy is also no assurance against gallstones. Marks and Bank *(20)* reported 8 patients who had emergency laparotomy for acute pancreatitis. In 5 of these, no stones were felt in the gallbladder despite careful palpation. Subsequently, all 5 were shown to have gallstones, either by x-ray or by repeat operation.

B. *In Alcoholic Pancreatitis:*

1) Internal surgical drainage of pseudocysts - usually uncomplicated in the short run, but almost half the patients continue to have pain months and years later *(22)*.

2) Duodenectomy and sphincterectomy
3) Celiac ganglion blocks
4) Splanchnicotomy

} Do not relieve pain in the alcoholic *(21-27)*

5) Pancreaticoduodemectomy
6) Roux-En-Y pancreaticojejunostomy
7) 95% pancreatic resection

} Relieve pain in 60-80% *(21-27)*

	Rate Mortality	Late Deaths	Good to Fair Results
Pancreaticoduodenectomy	6%	22%	62%
Roux-En-Y	2%	25%	80%
95% resection	2%	25%	73%

Note: These results are from centers specializing in pancreatic surgery.

The large numbers of late deaths is the major problem with all three of these operations. The average time interval between operation and death was 3 years. Deaths are caused by continuing alcoholism, endocrine and exocrine insufficiency, malnutrition, suicide, GI hemorrhage, pneumonia, intestinal obstruction, and in some cases due to causes unrelated to pancreatic disease.

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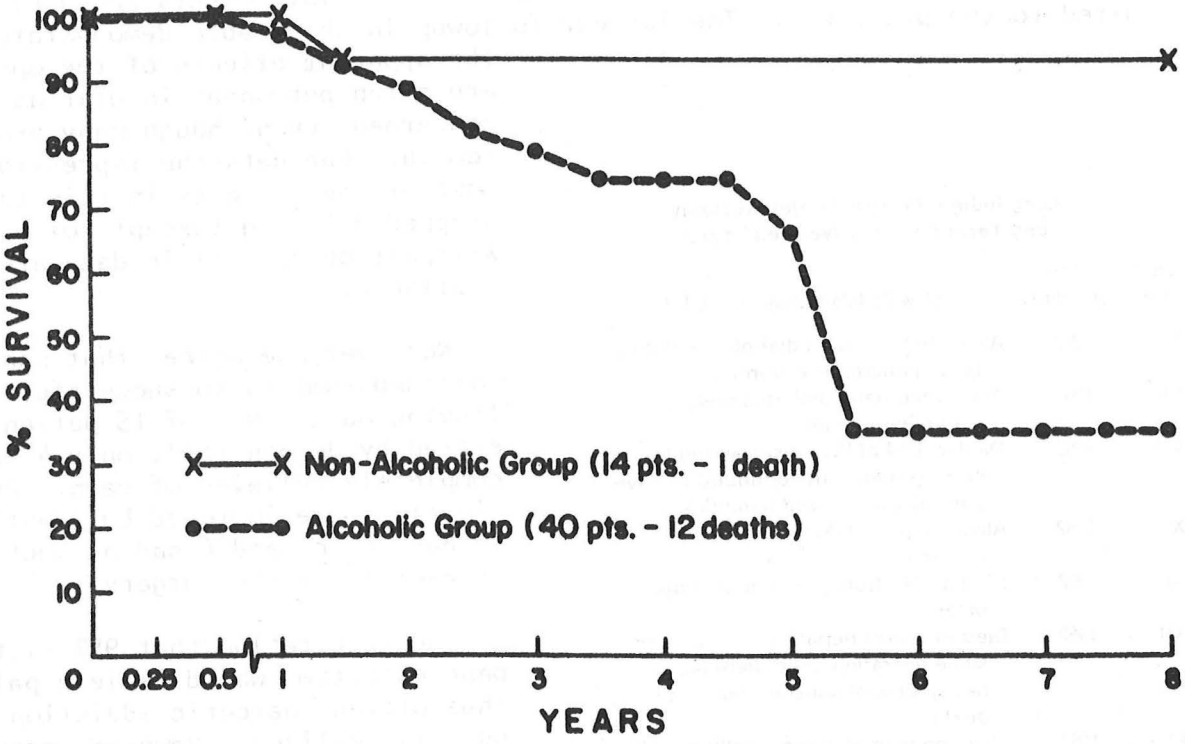

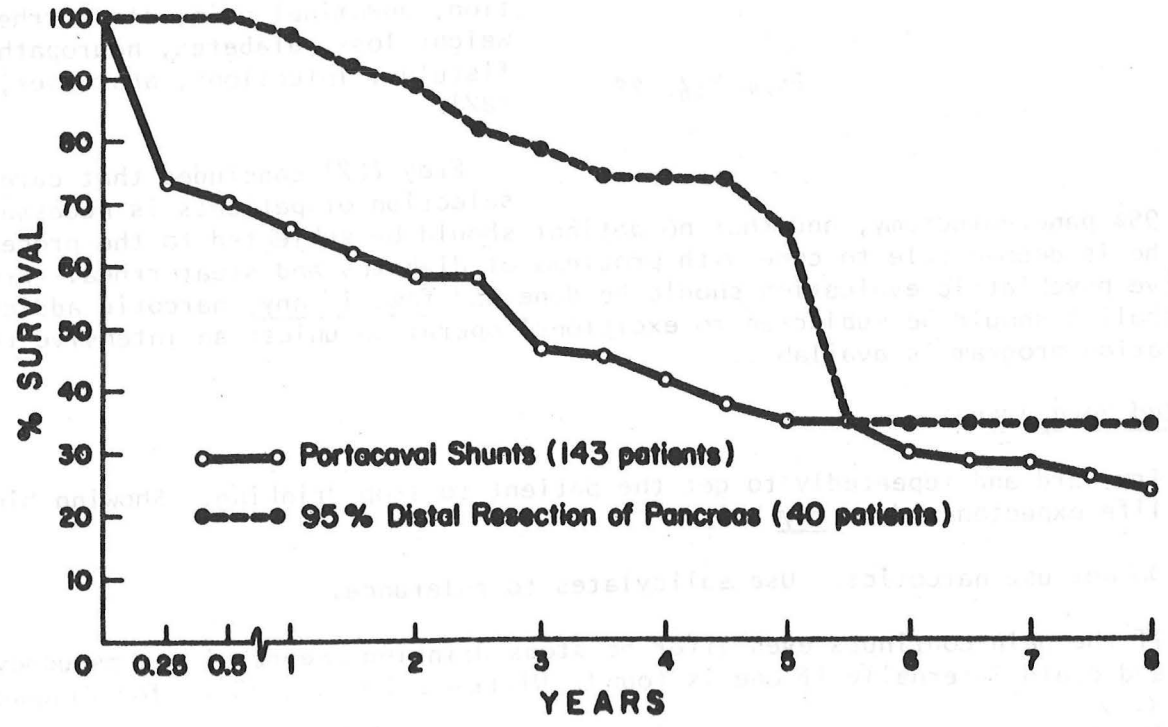

From Ref. 27

Good results from longitudinal pancreaticojejunostomy depend on the presence of dilated pancreatic ducts *(22)*. If done in patients with small ducts, this procedure will not relieve pain, and the communication of the ducts with the jejunum will only be temporary *(22)*. Most, but not all, alcoholics have dilated ducts and are, therefore, suited to the procedure. The 10-year followup in this table demonstrates that the apparent effects of the operation are often permanent insofar as pain is concerned, even though many problems remain. One gets the impression that most of the patients in this table had stopped drinking (except for patient XII), although specific data are not available.

Longitudinal Pancreaticojejunostomy: Long-Term Results (Over Ten Years)

Patient Number*	Date of Operation	Follow-Up Information through 1972
V	1962	Alive; no pain; mild diabetes mellitus; takes pancreatic enzymes
VI	1961	Alive; mild pain; diabetes mellitus controlled by diet
VII	1962	Died in 1964 of liver disease; moderate improvement but continued to have pain which required narcotics
X	1962	Alive; no pain; taking pancreatic enzymes
XI	1962	Died in 1969 from a bleeding peptic ulcer
XII	1962	Died in 1969 in hepatic coma; no pain since operation; mild diabetic; heavy alcohol consumption until death
XIII	1962	Alive; no pain; diabetes mellitus well controlled with insulin; taking pancreatic enzymes
XIV	1962	Alive; no pain; no medications

From Ref. 22

Not everyone agrees that pancreaticojejunostomy is so successful in relieving pain. Out of 15 patients operated by Jordan *(25)*, only 4 were completely relieved of pain. An additional 5 were improved but continued to have pain, and 6 had as much pain as ever after the surgery.

The expectation that 95% distal pancreatectomy would relieve pain and thus prevent narcotic addiction is usually realized. However, many hospital admissions are necessary for alcoholism, GI bleeding, hepatitis, duodenal ulcer, intestinal obstruction, abdominal pain, steatorrhea, weight loss, diabetes, neuropathy, fistulas, infections, abscesses, etc. *(27)*.

Frey *(27)* concludes that careful selection of patients is necessary before 95% pancreatectomy, and that no patient should be subjected to the procedure unless he is deemed able to cope with problems of diabetes and steatorrhea. Preoperative psychiatric evaluation should be done and few, if any, narcotic addicts or alcoholics should be subjected to excisional operation unless an intensive rehabilitation program is available.

Suggested Management:

1) Try hard and repeatedly to get the patient to stop drinking. Showing him the life expectancy data may help.

2) Do not use narcotics. Use salicylates to tolerance.

3) If the pain continues even after he stops drinking, search for a pseudocyst and drain internally if one is found. Ultrasound is excellent for diagnosis *(50)*.

4) Don't rush into more extensive pancreatic surgery, even if pain continues. Try to tide the patient over, hoping for a spontaneous remission.

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5) If the situation is intolerable, and something must be done, do a retrograde pancreatogram (pancreatograms should not be undertaken lightly since they may cause pancreatitis, which at times may be fatal).

   a) If ducts are dilated, have a specialist do a longitudinal pancreaticojejunostomy.

   b) If the ducts are not dilated, consider a 95% pancreatectomy by a specialist, provided the patient is not addicted to narcotics and is not continuing to drink. Few, if any, patients should reach this stage, since most alcoholics will have dilated ducts. Furthermore, if they don't stop drinking and narcotics, Frey does not think the operation should be done.

6) As an alternate to surgery, large doses (1,000 to 5,000 rad) of high voltage irradiation should be considered. Werner and Wetterfors (*49*) report that 6 of 9 patients with chronic painful pancreatitis were relived of pain by this treatment (average followup 2 years). Alleviation of pain seemed to be greatest when the exocrine function of the pancreas before treatment was low.

CHRONIC PANCREATITIS SIMULATING PANCREATIC CANCER

Case Reports from PMH and Dallas VAH:

Case 1: Autopsy Case No. 6.

Case 2: R.J., 54 y/o, non-alcoholic: He developed pruritis and obstructive jaundice without abdominal pain. Preoperatively the gallbladder was ? palpable. At operation in June of 1974 a 3 x 3 x 2 cm hard mass was felt in the head of the pancreas. The common duct and gallbladder were distended. There were no enlarged nodes or metastatic lesions. Operative cholangiogram showed complete obstruction of the distal part of the common duct near the ampulla. A Whipple procedure was done. The patient was discharged 1 month later.

Path Report: Head of pancreas measuring 4 x 4 x 6 cm. Diffuse induration. No tumor nodule. Microscopic examination disclosed fibrotic scarring of the pancreas due to chronic pancreatitis. No malignancy could be found after extensive histologic search.

Comment: Chronic pancreatitis simulating discrete pancreatic cancer. Etiology of pancreatitis unknown. Radical surgery for non-malignant disease.

Case 3: 42 y/o M: Admitted with hematuria secondary to prostatitis. Routine studies revealed a high alkaline phosphatase. The patient was a heavy alcoholic until 3 months PTA, and he often developed abdominal pain after ingestion of alcohol. He had had no pain in past 3 months, since he gave up drinking. Physical exam was negative. The serum bilirubin was initially 0.5 and later 2.0. The SGOT was 171-208. The alkaline phosphatase was 155 K.A. units. The LAP was 2000. Four serum amylase concentrations were normal (20-96). Liver scan and gallbladder series were normal. Clinical impressions were hepatoma, pancreatic cancer, granulomatous liver disease and intrahepatic cholestasis. A retrograde cholangiogram was attempted but all the dye entered the pancreatic duct, revealing a "chain of lakes", strongly suggestive of chronic pancreatitis. Still, the clinical diagnosis was probable malignancy.

At surgery in May of 1974 an operative cholangiogram revealed total occlusion of the common bile duct. A h ard mass was felt in the head of the pancreas. The gallbladder was scarred. No evidence of metastasis was noted. The impression was carcinoma of the head of the pancreas, and a Whipple procedure was done. During the course of this surgery, the portal and splenic veins were lacerated, and the patient developed hemorrhagic shock and died postoperatively.

Path Report: Severe chronic pancreatitis. No malignancy after exhaustive histologic search.

These three patients illustrate the fact that benign pancreatic disease, or even a normal pancreas (Case 1), can simulate cancer of the head of the pancreas

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to such a degree that excellent surgeons will perform a Whipple procedure. Several authors *(56, 57)* have emphasized that complete obstruction of the common bile duct is practically pathognomonic of pancreatic cancer and is strong evidence against chronic pancreatitis as a cause of obstructive jaundice. Cases 2 and 3 illustrate the fallacy of such statements [assuming that these patients don't have a cancer that was missed by the pathologic examination, which has occasionally been reported (see discussion in Ref. 57)] and Hess *(58)* is quoted by Guien *(56)* as finding that complete stenosis of the common duct would be present in 9.3% of cases of chronic pancreatitis.

Why are Whipple procedures done for "cancer" of the pancreas without histologic proof of malignancy? The answer is three-fold. First, many surgeons have emphasized the dangers and unreliability of pancreatic biopsy (See Refs. 59 and 57). The complications in some series are as high as 20%, and they include fistulas, hemorrhage, abscess, and postoperative mortality, and the theoretic danger of spreading cancer. Second, the results of pancreatic biopsy are considered to be unreliable (average 65% correct), with many false-negatives. Therefore, a negative biopsy should not prevent a Whipple procedure, if the clinical diagnosis of pancreatic cancer seemed secure. And, third, pancreatic surgeons have found that they can make a correct clinical diagnosis at the operating table in 95% of the cases *(58)*.

Apparently, most surgeons do not insist on a positive tissue diagnosis before proceeding with a Whipple procedure for cancer of the pancreas and periampullary region *(60)*. However, even surgeons who specialize in pancreatic surgery can be wrong. For example, Warren and Cattell *(63)* did pancreatico-duodenectomies for benign disease in 6 of 218 patients (about 3%). In the hands of excellent surgeons who are not pancreatic specialists, this incidence would probably be much higher. Gilchrist, quoted in Ref. 61, found 7 instances in Chicago in a single year. Decker *(44)* reported 77 patients who had Whipple procedures without biopsy with an operative diagnosis of ampullary carcinoma. Three turned out not to have cancer, and two of these died postoperatively. Other reports of deaths from Whipple procedures for benign lesions are contained in Refs. 45, 46, and 47.

Not all workers agree that pancreatic biopsy is especially dangerous or unreliable, and many think that histologic proof of malignancy is mandatory before radical pancreatic surgery for cancer. Some studies whose results favor the use of pancreatic biopsy are summarized below.

1) *Forsgren (43) - 50 Pancreatic Biopsies:*

Frozen Section Reading - 38 Cases

29 Cases with Verified Carcinoma	
"Cancer"	26
Suspicion of cancer	2
Normal Pancreas	1
9 Cases Verified Not to Have Carcinoma:	
Cancer	1
Pancreatitis	5
Normal pancreas	3

Paraffin Section - 50 Cases

38 Cases with Verified Carcinoma:	
"Cancer"	35
Suspicion of cancer	2
Normal pancreas	1
12 Cases Verified Not to Have Carcinoma:	
Cancer	1
Pancreatitis	5
Normal pancreas	5
Nonspecific	1

Forsgren highly recommends biopsy before the decision is made to proceed with radical surgery for pancreatic "cancer". He reported only one complication (abscess) in 50 patients.

2) Decker (*44*) is another worker who has reported generally good results from pancreatic biopsy. He did wedge biopsy in 74 patients and aspiration biopsy in 7. Frozen section diagnosis was correct in 70% of the cases, and paraffin section was correct in 82%. The diagnosis was false-negative in 6 patients who had cancer. There were no false-positive diagnoses. In one case, the surgeon went ahead with Whipple procedure in spite of a negative frozen section report, and microscopic studies on the resected specimen showed no cancer. There were 3 complications in the 81 patients (abscess and hemorrhage).

3) Arnesjo (*48*) uses a small needle and does multiple aspirations for cytodiagnosis. Reports 18 cases with no false-positives, and 2 false-negatives. The risks are negligible, even with a large number of punctures into deeply located lesions. Considerable experience is necessary by the pathologist.

4) Gambill (*55*) - Mayo Experience: Concludes that pancreatic biopsy is not especially dangerous and that they should be done before Whipple procedure for cancer.

	Overall Mortality	Abdominal Cause of Mortality
Exploration and pancreatic biopsy without other procedure n = 48	4.2%	1.9%
Exploration and biopsy of metastatic lesion without other procedure n = 84	4.8%	3.6%

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5) Longmire *(60)* states that "although we do not insist on a positive tissue diagnosis in every case, we have usually obtained a biopsy of malignant tissue before proceeding with resection in our patients". He considers a positive biopsy essential prior to resection of small lesions of the pancreas.

After considering the pros and cons of pancreatic biopsy and the overall results of surgical therapy of pancreatic and peripancreatic cancer *(63)*, the following conclusions were reached by the author:

1) Whipple procedures should only be done by surgeons who specialize in pancreatic surgery. Otherwise, the operative mortality will be excessively high and too many benign lesions will be mistaken for malignant disease. If a nonspecialist encounters what is thought to be a resectable cancer, he should decompress the biliary tract and refer the patient to a pancreatic specialist.

2) If a pancreatic surgeon is certain he is dealing with a periampullary cancer (some of these will be small tumors in the head of the pancreas, some will be ampullary, bile duct or duodenal cancers) of less than 2.5 cm in diameter including its surrounding inflammatory reaction, it is reasonable for him to do a Whipple procedure even if a biopsy is negative. If there is any doubt in his mind about the malignant nature of the lesion, he should not do a Whipple procedure unless a biopsy shows proof of malignancy.

3) Newer methods of biopsy should be utilized to see if recent good reports can be confirmed. If false-negative results can be reduced to a low level by a safe biopsy technique, radical surgery could be reserved for cases where histologic proof of malignancy has been obtained.

4) Cancers that are recognized grossly as being in the head of the pancreas (and are not, therefore, periampullary) should not be treated by Whipple procedure. The operative mortality is too high and the clinical results too poor to warrant this procedure.

If these guidelines are followed, few Whipple procedures for benign disease will be done, patients with periampullary cancer will be given a chance for long-term survival (25-30%) and better paliation, and patients with cancer of the pancreatic head will not be subjected to useless and very dangerous surgery.

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