Acute Pancreatitis

Büchler · Uhl · Malfertheiner · Sarr

Diseases of the Pancreas

Chronic Pancreatitis

Neoplasms of the Pancreas

KARGER

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Dedicated to our wives
Hedi, Regina, Karin and Barbara

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Contents

Abbreviations

AIP	Acute interstitial edematous pancreatitis
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
APACHE II	Applied Physiology And Chronic Health Evaluation Score
ARDS	Adult respiratory distress syndrome
AST	Aspartate aminotransferase
α_1-AT	α_1-Antitrypsin
ATP	Adenosine triphosphate
BE	Base excess
BG	Blood glucose
BII	Bilroth II resection
BUN	Blood urea nitrogen
CA 19-9	Tumor marker
cAMP	Adenosine monophosphate
CAPAP	Cyclic activation peptide of carboxypeptidase B
CAPD	Continuous ambulatory peritoneal dialysis
CCE	Cholecystectomy
CCK	Cholecystokinin
CE	Carboxylesterase
CEA	Carcinoembryonic antigen
CEH	Carboxylester hydrolase
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CGRP	Calcitonin gene-related peptide
COX II	Cyclooxygenase II
CRP	C-reactive protein
CT	Computed tomography
CVC	Central venous catheter
CVP	Central venous pressure
D	Dalton
DDI	2',3'-Dideoxyinosine
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
ECL cells	Histamine-producing cells
EF	Efficacy factor
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EPT	Endoscopic papillotomy
ERC	Endoscopic retrograde cholangiography
ERCP	Endoscopic retrograde cholangiopancreatography
ERP	Endoscopic retrograde pancreatography
ESWL	Extracorporeal shock wave lithotripsy
EUS	Endoscopic ultrasonography
FiO_2	Inspiratory oxygen concentration
FIP	Fédération Internationale Pharmaceutique
FNA	Fine-needle aspiration
FNP	Fine-needle puncture
FNP+	Fine-needle puncture positive for organisms
G	Giga, decimal prefix for 10^9
G-CSF	Granulocyte colony-stimulating factor
GEP	Gastroenteropancreatic
GI	Gastrointestinal
γ-GT	γ-Glutamyl transpeptidase
HC	Hematocrit
HLA-haplotypes	Histocompatibility antigen-gene complexes
hPASP	Human pancreas-specific protein
IAPP	Insulin-like amyloid polypeptide
ICU	Intensive care unit
IDDM	Insulin-dependent diabetes mellitus
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-8	Interleukin 8
IMC	Intermediate care
INR	International normalized ratio
IPMN	Intraductal papillary mucinous neoplasm
IU	International units
IVF	Intravenous fluids
LDH	Lactate dehydrogenase
LH-RH analogues	Luteinizing hormone-releasing hormone analogues
LSS	Lumbar spine syndrome with radicular pain
α_2-M	α_2-Macroglobulin
MCT	Medium-chain triglycerides
MCV	Mean corpuscular volume of erythrocytes
MEN	Multiple endocrine neoplasia
MOF	Multi-organ failure

MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
NAD	Nothing abnormal detected
NBT-PABA test	N-benzoyl-*L*-tyrosyl-*p*-amino-benzoic acid test
NCT	Normal-chain triglycerides
NET	Neuroendocrine tumors
NP	Necrotizing pancreatitis
NPO	Nothing per os
OGTT	Oral glucose tolerance test
ORC channels	Outward rectifying chloride channels
PAF	Platelet- activating factor
PBC	Primary biliary cirrhosis
PCA	Patient-controlled analgesia
pCO_2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PCT	Procalcitonin
PEEP	Positive end-expiratory pressure
PET	Positron emission tomography
PLA_2	Phospholipase A_2
PLT	Pancreolauryl test
PMN elastase	Polymorphonuclear elastase
pO_2	Arterial partial pressure of oxygen
PP	Pancreatic polypeptide
PPOm	Pancreatic polypeptidoma
PP-Whipple	Pylorus-preserving partial pancreaticoduodenectomy
PSC	Primary sclerosing cholangitis
PSTI	Pancreatic secretory trypsin inhibitor
PTC	Percutaneous transhepatic cholangiography
PTCD	Percutaneous transhepatic cholangio-drainage
PTT	Partial thromboplastin time
SAPS	Simplified Acute Physiology Score
SIRS	Systemic inflammatory response syndrome
SP	Substance P
TAP	Trypsinogen-activating peptide
TGF	Transforming growth factor
TNM	Tumor-staging system
TPN	Total parenteral nutrition
U	Unit(s)
UICC	Union Internationale Contre le Cancer
US	Ultrasonography
VRE	Vancomycin-resistant enterococcus

Preface

Following its publication in 1996, our book *Pankreaserkrankungen* (*Diseases of the Pancreas)* met with a great response. However, in the intervening seven years, the first German edition has lost its timeliness. We have summarized the vast amount of new knowledge gained in the interval in this revised edition now in its first English translation. Besides the readers, our thanks are due to the many reviewers for their praise and criticism, which are reflected in this interdisciplinary American and European revision. The new, completely revised second edition represents a summary of the evidence-based literature and the authors' own expertise in the field of diseases of the pancreas over many years. We have included up-to-date data on the diagnosis and treatment of acute pancreatitis. Besides the new necrosis markers, we have paid particular attention to techniques of imaging by means of magnetic resonance tomography and to the various randomized controlled studies on treatment.

In the chapter on chronic pancreatitis, we revised the etiology and classification and dealt in considerably greater depth with clinical aspects, pancreatic function and imaging procedures, including new clinical studies on evidence-based treatment.

With regard to pancreatic neoplasms, we focused on imaging with the use of the newer technique of spiral CT and the ultra-fast magnetic resonance tomography of the 'all-in-one' technique. The latter permits the simultaneous visualization of morphology and the state of blood vessels and ducts. Particular attention has been paid to aspects that will be of increasing importance in the future, i.e. molecular biology and gene polymorphisms that may explain many of the diverse individual responses to different disease states. At the end of the book, there is a comprehensive list of references, divided according to criteria of evidence-based medicine, to give readers an opportunity to study the relevant papers themselves. We deliberately refrained from incorporating references into the text in order not to interrupt the flow of reading.

This second, fully revised, edition is designed to go beyond subject boundaries in order to serve the welfare of our patients with diseases of the pancreas.

Heidelberg/Bochum/Magdeburg/
Rochester, Minn.
in 2004

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Acute Pancreatitis

Case 1

Male, 24, married, 2 children, employed as a bricklayer,
history of controlled alcohol abuse for years

History

The patient went to his family doctor's office on Monday morning. The previous day he had taken part in a celebration and had consumed large amounts of alcohol. During the night he developed severe epigastric pain which radiated through to the back. While still at home, the patient had taken 1,300 mg acetominophen and 2 oz of Peptobismol orally. This had not produced any real alleviation of the pain. Since then, the epigastric pain had increased dramatically in severity and the patient was brought to the office by his wife with an urgent plea for pain relief.

Findings

The patient was diaphoretic and flushed. On examination of the abdomen, the patient complained of severe epigastric pain radiating to the back. The abdomen was tense in the epigastric region but without true peritonitis. Marked tenderness in the epigastrium. Doughy swelling palpable in the upper abdomen. Auscultation of the abdomen revealed no bowel sounds. Percussion indicated tympany.

Body weight 80 kg (170 lb), height 181 cm (6 ft).
Body temperature (rectal) 37.9°C, heart rate 105/min, blood pressure 150/105 mm Hg.
Laboratory Parameters: Hemoglobin 14.5 g/dl, leukocytes 13.5 × 10^9/l, amylase 2,025 U/l, AST 18 U/l, ALT 21 U/l, γ-GT 85 U/l, alkaline phosphatase 95 U/l, glucose 93 mg/dl, bilirubin 10 mg/dl, creatinine 1.1 mg/dl, sodium 138 mEq/l, potassium 4.4 mEq/l, calcium 2.2 mmol/l, CRP 35 mg/l.

Transabdominal Ultrasonography

Marked intestinal gas, which made the overall situation difficult to assess. Liver enlarged, suspected fatty degeneration, gallbladder unremarkable, in particular no indication of gallstones. Extrahepatic bile ducts not dilated. Pancreas: only the body visualized, structure spongy, gland appeared enlarged and swollen. No sign of dilatation of the pancreatic duct, no calcifications, no sign of tumor, no free fluid in the abdomen.

Diagnosis

Acute edematous pancreatitis, probably alcohol-induced.

Management

Intramuscular injection of 20 mg meperidene in the family doctor's office, then admission to hospital for in-patient care.

Course

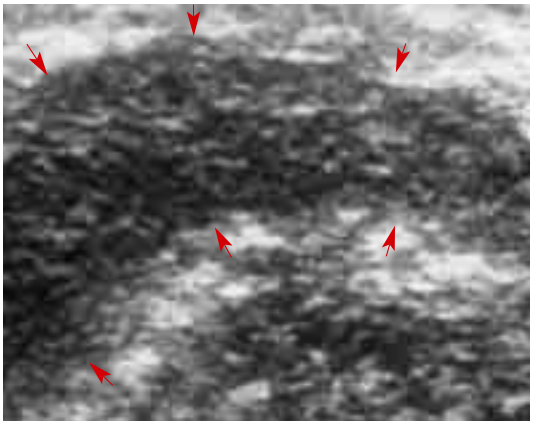
In hospital, admission to the Department of Internal Medicine (observation ward). Placement of a bladder catheter and central venous catheter. NPO. Continuous analgesic therapy with meperidine patient-controlled analgesia intravenously. Daily checks of CRP, which never rose above 50 mg/l. Intravenous hydration with crystalloid solutions: day 1 and day 2 each 4.5 liters/24 h, day 3 reduction to 3 liters/24 h. This treatment resulted in relief of pain within 24 h. The patient recovered rapidly. The serum amylase returned to the normal range on day 4. Resumption of food by mouth on day 5 with tea, followed by a gradual build-up to a complete diet on day 8. ERCP on day 9 showed a normal pancreatic ductal system without signs of stricture, cysts or extravasation of contrast medium. The patient was discharged on day 10 in good general condition.

Prognosis

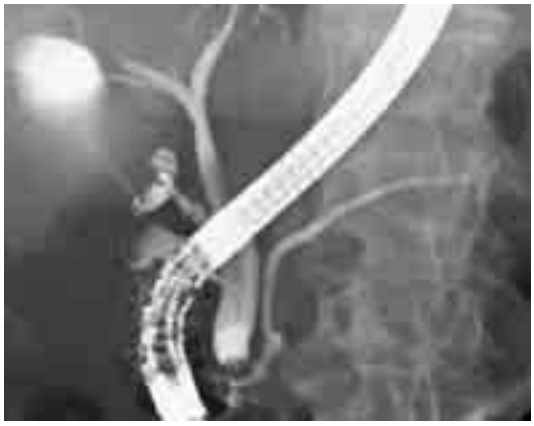
If the patient refrains from alcohol, the prognosis is good. However, in view of the patient's work and social situation, this is unlikely. Thus, there is a likelihood of recurrent bouts of acute pancreatitis.

Case Record

History	Excessive intake of alcohol 24 h previously (celebration)
Diagnosis	Acute pancreatitis
Etiology	Alcohol
Laboratory findings	Amylase 2,025 U/l CRP 35 mg/l No cholestasis
Transabdominal US	Normal gallbladder/bile ducts Edematous pancreatitis
Staging	Edematous (mild) form
Treatment	NPO IVF Bladder catheter
Course	Improvement in 7 days Discharge on day 10
Prognosis	Good, provided abstinence from alcohol



Transabdominal US showing edematous pancreatitis. Spongy organ structure with poorly defined organ margins (arrows).



ERCP showing normal biliary and pancreatic duct systems.

Case 2

Female, 64, married, 3 children, housewife

History

The patient had had 3 children. History of obesity from the age of 40. During a routine investigation, 2 years previously, transabdominal ultrasonography had revealed gallstones. The patient was admitted to hospital in the morning. On the previous evening, 20 min after her evening meal, slow onset of a constant pain had developed in the upper right abdomen and radiated to the right scapula. The patient had unsuccessfully tried oral acetominophen, but the pain slowly abated after about 3 h and she fell asleep. However, in the early hours of the morning onwards, a persistent, diffuse ache developed in the upper abdomen, especially in the epigastrium, radiating through to the back. She called her family doctor who, suspecting biliary colic, arranged for her to be admitted to hospital.

Examination Findings

The patient had her legs drawn up and could not lie flat on her back. She complained of severe persistent excruciating pain in the epigastrium as well as of nausea after vomiting twice.

The abdomen was very tender, especially in the epigastrium and under the costal margin on the right. She had mild epigastric peritoneal signs. Bowel sounds were absent. Sclerae were marginally icteric, the tongue dry and coated.

Body weight 90 kg (200 lb), height 175 cm (5 ft 9 in).
Body temperature (rectal) 38.2°C, heart rate 105/min, blood pressure 155/80 mm Hg.
Laboratory Parameters: Hemoglobin 12.6 g/dl, leukocytes 17.5 × 10^9/l, amylase 3,750 U/l, lipase 2,360 U/l, AST 105 U/l, ALT 98 U/l, γ-GT 65 U/l, alkaline phosphatase 314 U/l, bilirubin 0.8 mg/dl, creatinine 1.0 mg/dl, glucose 112 mg/dl, sodium 140 mEq/l, potassium 4.3 mEq/l, calcium 9.2 mg/dl, CRP 66 mg/l.

Transabdominal Ultrasonography

Gallbladder distended, with multiple calculi up to 0.8 cm in diameter. Extrahepatic bile ducts dilated to 9 mm. One calculus in the bile ducts could be clearly visualized. Pancreas with structural inhomogeneities, marked sponginess of the parenchyma seen as diffuse hypodense zones. Pancreas enlarged. Peripancreatic fluid present. Marked edema at the root of the mesentery, about 100 ml fluid in the pouch of Douglas.

Diagnosis

Acute edematous pancreatitis, probably due to gallstones.

Management

ERC ± papillotomy if appropriate.

Course

The patient was admitted to the floor of an internal medicine department. A bladder catheter and nasogastric tube were inserted and central venous access was established. An ERC was carried out after 4 h and revealed a dilated extrahepatic biliary system with several gallstones and a 0.4-cm gallstone impacted at the ampulla, which was extracted via papillotomy.

The symptoms improved 12 h after papillotomy and stone extraction. The treatment for the next 6 days consisted of no food by mouth and IVF (3–5 liters crystalloid solutions/day). After that, the diet was advanced, with obvious clinical recovery. Laparoscopic cholecystectomy on the 7th day after admission to hospital with an uncomplicated postoperative course. The patient was discharged on the 12th day after admission, with ongoing improvement of the clinical symptoms and normalization of the laboratory parameters. A follow-up ultrasonogram on day 10 showed the pancreas to be of normal size and structure with no significant peripancreatic fluid collections.

Prognosis

The patient may be regarded as fully recovered.

Case Record

History	Known gallstones 24 h previously, pain in the right upper abdomen
Diagnosis	Acute pancreatitis
Etiology	Gallstones
Laboratory findings	Amylase 3,750U/l AST 105 U/l CRP 66 mg/l Bilirubin 0.8 mg/dl
US	Cholelithiasis Edematous pancreatitis
Staging	Edematous (mild) form
Treatment	NPO IVF Bladder catheter ERC, papillotomy and stone extraction
Course	Improvement within 5 days Laparoscopic cholecystectomy on day 7 Discharge on day 12
Prognosis	Good, fully recovered

ERCP with gallstone in the common bile duct.

Gallbladder with multiple small gallstones in acute biliary pancreatitis.

Case 3

Female, 40, married, 1 child, office administrator

History

After excess intake of alcohol, the patient, who had a history of alcohol abuse, was admitted to a peripheral hospital in shock, with increasing abdominal pain for the previous 42 h. Because of rapid clinical deterioration and the diagnosis of severe acute pancreatitis necessitating impending mechanical ventilation, the patient was transferred to a referral hospital.

Findings

The patient was tachypneic, tachycardic, hypotensive and drowsy. Abdomen markedly distended and tympanitic.

Body weight 103 kg (226 lb), height 175 cm (5 ft 9 in).
Body temperature (rectal) 38.9°C, heart rate 132/min, blood pressure 95/55 mm Hg.
Laboratory Parameters: Hemoglobin 11.2 g/dl, leukocytes 16.5 × 10^9/l, INR –2.1, amylase 1,405 U/l, lipase 1,896 U/l, AST 29 U/l, γ-GT 115 U/l, creatinine 3.1 mg/dl, calcium 7.6 mg/dl, blood sugar 312 mg/dl, CRP 347 mg/l, blood gas analysis: pO_2 62 mm Hg on 6 liters O_2/min, pH 7.3, pCO_2 31.4 mm Hg, base excess –11.

Transabdominal Ultrasonography

Evidence of cholelithiasis and fatty liver. Pancreatic region not able to be visualized due to massive overlay of intestinal gas.

Contrast-Enhanced CT

Evidence of acute necrotizing pancreatitis with necrosis of about 50% of the pancreas, especially in the body and head, with normal perfusion of the tail of the pancreas. Extensive peripancreatic necrosis with extension behind the right and left colon. Free intra-abdominal fluid. Clear signs of ileus with distended loops of small and large bowel.

Diagnosis

Necrotizing pancreatitis with multi-organ failure (pulmonary, renal, cardiovascular, coagulation, cerebral).

Management

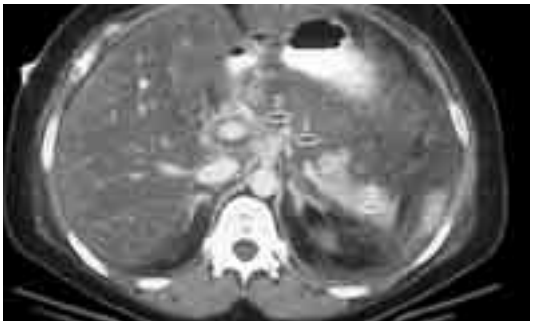
Transfer to the ICU.

Course

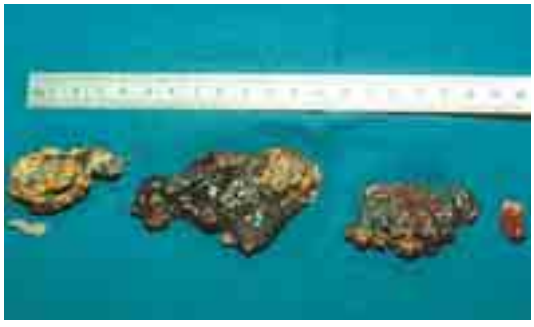
The patient was intubated for controlled mechanical ventilation with an FiO_2 of 80% and a PEEP of 10 mm Hg. Conservative treatment was continued – NPO, nasogastric intubation, bladder catheter and IVF depending on the CVP. Initiation of prophylactic intravenous antibiotic therapy with imipenem and cilastatin, TPN, and exogenous insulin therapy. Crystalline infusion solutions were increased for oliguria, with initially 6 liters/24 h; in addition, administration of furosemide 200 mg/24 h. Norepinephrine, 7 µg/kg/min, was administered for hypotension, and low dose dopamine, 1–4 µg/kg/min, was added to increase renal blood flow. The patient's condition stabilized over the initial 2 weeks, but on day 18 cardiovascular deterioration occurred with signs of sepsis. A CT was obtained with FNA of peripancreatic fluid collection. Gram stain revealed gram-negative microorganisms and subsequent culture was positive for *Escherichia coli*, *Proteus* and *Candida*. Laparotomy with removal of the pancreatic and retroperitoneal necrosis. The patient subsequently recovered rapidly and, 3 weeks later, was able to leave the ICU with intact, closed, continuous retroperitoneal lavage. Progressive decrease in lavage volume, resumption of oral diet, and patient mobilization. Insulin therapy no longer needed. Another 2 weeks later, development of temperatures of up to 39°C and elevated inflammatory parameters. CT showed a retrocolic fluid collection (abscess) on the right, interventional percutaneous drainage carried out at the same session. Removal of the abscess drainage catheter 10 days later. Discharge after 56 days. A pancreatic fistula with up to 50 ml/day slowly decreased and stopped over the following 2 months.

Case Record

History	Transfer to referral hospital
Diagnosis	Acute pancreatitis
Etiology	Alcohol
Laboratory findings	Hemoglobin 11.2 g/dl, leukocytes 16.5×10^9/l, amylase 1,405 U/l, creatinine 3.1 mg/dl, calcium 7.6 mg/dl, blood sugar 312 mg/dl, INR –2.1, CRP 347 mg/l, blood gas analysis: pO_2 62 mm Hg on 6 liters O_2/min, pH 7.3, pCO_2 31.4 mm Hg, base excess –11
CT	Pancreatic necrosis (50%) and extensive peripancreatic necrosis
Staging	Necrotizing pancreatitis
Treatment	ICU Mechanical ventilation Prophylactic antibiotics
Surgery	Necrosectomy and retroperitoneal lavage
Course	Interventional abscess drainage, spontaneous closure of a persistent pancreatic fistula after 2 months, decreasing insulin requirements
Prognosis	Good, recovery of pancreatic function



Contrast-enhanced CT: Necrosis of the head (2) and body (1) of the pancreas; tail (3) well perfused.



Infected pancreatic necroses.

An Atypical Case

Male, 49, married, computer scientist

History

The patient's family doctor arranged for his admission to hospital as an emergency with a suspected diagnosis of myocardial infarction. For the past 4 h, he had been complaining of pain in the left upper abdomen which radiated to the left half of the chest. This was the first occurrence of such symptoms, there had been no previous illnesses and no prior surgery.

Examination Findings in Hospital

The patient was tachycardic without signs of arrhythmias or irregular rhythm, and was hypotensive and tachypneic. Abdomen soft with epigastric tenderness.

Body weight 52 kg (115 lb), height 175 cm (5 ft 9 in).
Body temperature (rectal) 37.5°C, heart rate 110/min, blood pressure 95/70 mm Hg.
Laboratory Parameters: Leukocytes 14.3 × 10^9/l, amylase 3,830 U/l, lipase 7,790 U/l, AST 49 U/l, ALT 93 U/l, CRP 390 mg/l. All other laboratory parameters, including creatine kinase, were in the normal ranges.

ECG

Sinus tachycardia; otherwise normal ECG without signs of myocardial infarction or arrhythmia.

Transabdominal Ultrasonography

Normal appearance of the gallbladder without signs of cholelithiasis. No dilatation of the intrahepatic or extrahepatic bile ducts. The pancreas could not be visualized because of gas overlay.

Contrast-Enhanced CT

Demonstration of severe acute pancreatitis with patchy pancreatic parenchymal necrosis and inflammation, especially in the left anterior pararenal space.

Diagnosis

Necrotizing pancreatitis of unknown etiology.

Management

Admission to the ICU, aggressive monitoring and early ERCP.

ERCP

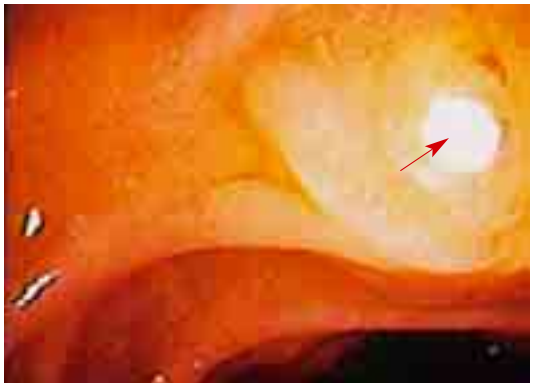
This study showed the major duodenal papilla to be normal with a normal extrahepatic biliary system. The presence of pancreas divisum, however, meant that only a short section of the main pancreatic duct could be visualized. The minor duodenal papilla was edematous with an impacted whitish calculus. A catheter was advanced via this obstacle into the minor papilla and Santorini's duct was dilated. Retraction of the catheter with the balloon inflated resulted in the removal of the stone from the papilla, with prompt drainage of the contrast medium and pancreatic juice.

Course

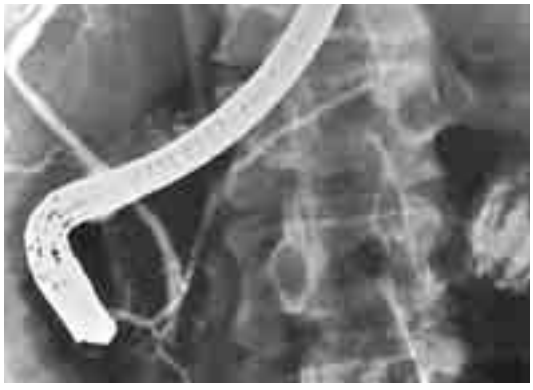
The patient made a rapid recovery over the next 4 days without any clinically important organ failure. The initial TPN was discontinued and replaced by a rapid advancement to a normal diet. The patient was ready to be discharged after 16 days. He has now been free from symptoms for 2 years, without a further attack of acute pancreatitis.

Case Record

History	Admission with suspected myocardial infarction
Diagnosis	Necrotizing pancreatitis
Etiology	Calculus in the minor duodenal papilla in the presence of pancreas divisum
Laboratory findings	Leukocytes 14.3 $\times 10^9$/l, amylase 3,830 U/l, lipase 7,790 U/l, AST 49 U/l, ALT 93 U/l, CRP 390 mg/l, all other laboratory parameters, including creatine kinase, were within the normal ranges
CT	Pancreatic necrosis ($<$30%)
Staging	Necrotizing pancreatitis (sterile necrosis)
Treatment	ICU, maximum conservative treatment
ERCP	Extraction of stone from the minor duodenal papilla
Course	No complications, good prognosis If appropriate, papillotomy of the minor duodenal papilla if the symptoms recur



Endoscopic view of the minor duodenal papilla showing the impacted stone (arrow).



ERCP with imaging of pancreas divisum.

Definition and Classification

The definition of acute pancreatitis reflects many years of work in an attempt to develop a classification of acute pancreatitis that is both clinically useful in directing therapy and allows different institutions and countries to compare patient populations and treatments with unified definitions. The basis for the current definition was created at the second Consensus Conference held in Marseilles in 1984 on the classification of acute pancreatitis. That classification was developed further in Atlanta in 1992, with particular reference to advances in diagnostic imaging and evaluation of the clinical severity of the disease.

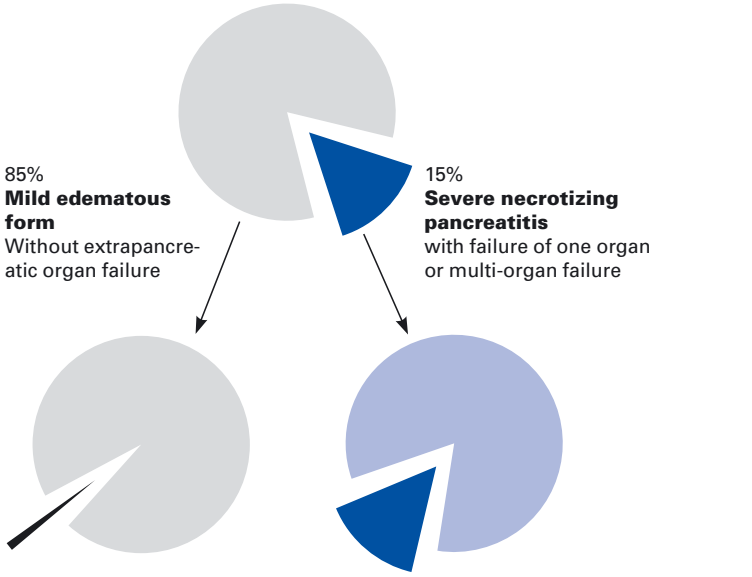
The three important aspects of the disease are the *clinical syndrome*, the *morphologic lesions* and the *loss of function*.

The *diagnosis* of acute pancreatitis is based on *acute abdominal pain* in conjunction with a rise of at least the normal values of pancreas-specific *enzymes in the blood and urine*. In the majority of patients (about 85%), the disease takes a mild course (edematous pancreatitis) with complete disappearance of the clinical symptoms within just a few days. In a small group of patients (about 15%), the condition takes a severe course (necrotizing pancreatitis) due to the occurrence of dysfunction involving at least one organ system (cardiovascular system, lungs or kidneys). The most serious form culminates in multi-organ failure with death.

Acute pancreatitis may occur as a new event or as a recurrent condition.

Morphologically, we distinguish between an *interstitial edematous* and a *necrotizing* form of acute pancreatitis. *Edematous pancreatitis* may be accompanied by minimal retroperitoneal inflammation and a peripancreatic fluid collection; about 20% of the time, this peripancreatic fluid collection may be secondary to a disruption of the pancreatic ductal system and later (>4 weeks) develop into a pancreatic pseudocyst. In contrast, *necrotizing pancreatitis* is characterized by pancreatic parenchymal necrosis and/or necrosis of the retroperitoneal peripancreatic fat. The necrosis may be localized or affect the entire pancreas. The fatty-tissue necrosis is usually much more pronounced in the peripancreatic region. The necrotic regions may remain sterile or become infected, which has a crucial bearing on the subsequent clinical course of the disease. Sequelae of acute necrotizing pancreatitis include pseudocysts and pancreatic abscesses which can be distinguished 4–6 weeks after the acute event as late forms of acute pancreatitis. Both are as a rule space-occupying lesions and enveloped in a pseudocapsule. The development of localized colonic necrosis is a rare complication of necrotizing pancreatitis.

Morphology and Course



Definition

Acute upper abdominal pain
Marked (>3-fold) rise in the pancreatic enzymes in the blood (amylase, lipase)

Classifications

Atlanta 1992	Ulm 1987
I Acute pancreatitis	I Acute interstitial edematous pancreatitis
II Mild acute pancreatitis	II Acute necrotizing pancreatitis
III Severe acute pancreatitis	Sterile necrosis
IV Acute accumulation of fluid/ fatty tissue necrosis	Infected necrosis
V Pancreatic necrosis	III Pancreatic abscess
VI Pseudocyst	IV Postnecrotic pseudocyst
VII Pancreatic abscess	

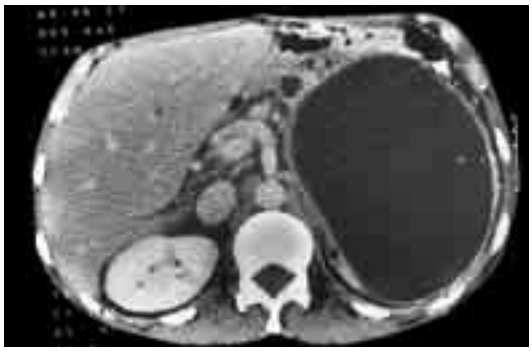
In acute pancreatitis, both exocrine and endocrine *pancreatic function* is affected, depending on the extent of the morphologic damage. In interstitial edematous pancreatitis, there is complete recovery of function of the gland (within 4–12 weeks), whereas after necrotizing pancreatitis, about half the patients are left with some element of pancreatic insufficiency, of varying degree, of exocrine and endocrine function.

An exact definition of the disease in terms of its clinical and morphologic features is important to define treatment of the acute condition as well as the resultant sequelae. It is only with the aid of a concise, accurate, and generally accepted terminology that there can be agreement between physicians around the world about this condition; universal acceptance of a unified terminology will allow development of improved therapies and a better understanding of the natural history of the spectrum of acute pancreatitis.

Pancreatic Necrosis

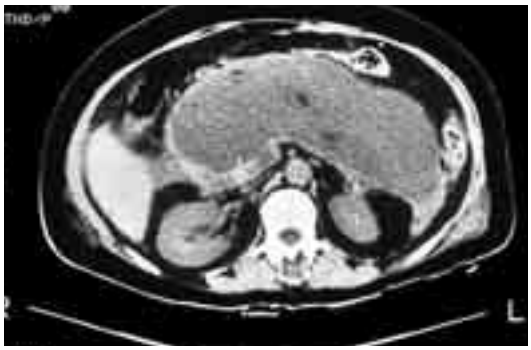
Macroscopic total necrosis.

Postnecrotic Pancreatic Pseudocyst



CT of a pancreatic pseudocyst after necrotizing pancreatitis.

Pancreatic Abscess



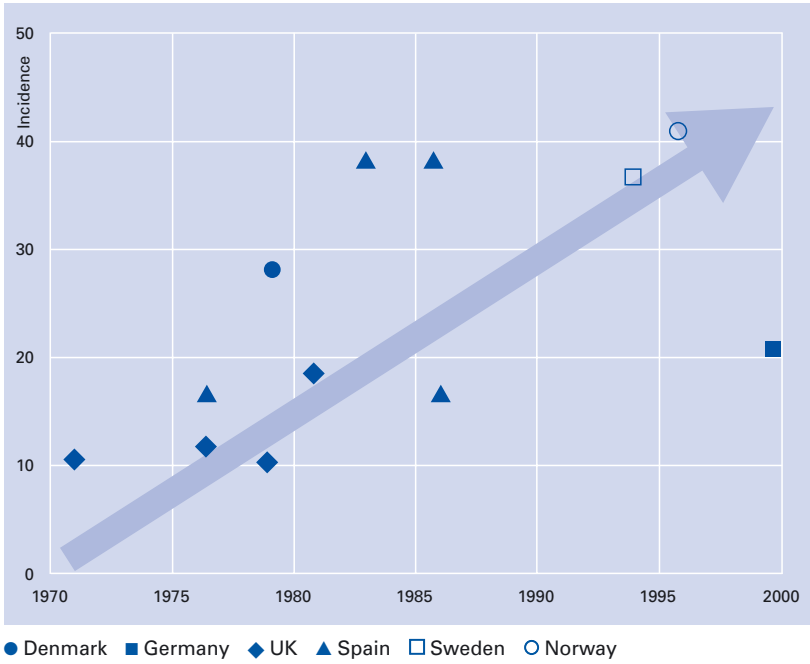
CT showing an abscess in the head of the pancreas and lesser sac.

Epidemiology

Only limited figures are available on the incidence and prevalence of acute pancreatitis in different population groups. For the USA and Great Britain, the incidence ranges from 11 to 23 patients/100,000 inhabitants. In Germany, in the urban district of Bonn, the incidence in 1994 was 22 patients with acute pancreatitis per 100,000 inhabitants. If episodes that should be regarded as recurrences of chronic pancreatitis are included, the number of patients requiring admission to the hospital for acute exacerbations of pancreatitis increases to about 40 patients/100,000 of the population. In view of the invariable presence of severe abdominal pain during an episode of acute pancreatitis, it is unlikely that many patients are diagnosed wrongly or treated by their family physician as an outpatient for nonspecific abdominal pain.

A high consumption of alcohol as well as the presence of cholelithiasis represent by far the majority of causes of acute pancreatitis (they jointly account for 80–90% of all cases of acute pancreatitis). In Germany, alcoholic and biliary etiologies are about equally balanced, whereas in Great Britain, for example, cholelithiasis is regarded as the primary factor (60%). Regional patterns are also prominent; inner city hospitals that take care of the indigent, often alcoholic population, see a much higher incidence of alcoholic pancreatitis, while more rural populations have a higher rate of gallstone-induced pancreatitis. While the first episode of alcohol-related acute pancreatitis affects primarily males and the peak incidence is between the age of 18 and 30 years, acute pancreatitis of biliary origin is relatively more frequent in females, the peak age range being 50–70 years. Acute pancreatitis takes a mild course in about 85% and a serious course in 15% of patients. As a result of improved diagnostic and therapeutic measures which can be directed at the special problems of individual patients, the mortality of acute pancreatitis has fallen below 10% in recent years, whereas as recently as the mid 1970s, it was as high as 20% or more. Currently, mortality related to acute pancreatitis is limited to patients with severe, acute necrotizing pancreatitis.

Incidence per 100,000 Inhabitants



Causes

Etiology

Although the list of factors that can potentially trigger acute pancreatitis is long, excess consumption of alcohol and the presence of gallstones predominate and, together, account for 80–90% of the episodes of acute pancreatitis. To provide a clearer overview of possible etiologic factors, it is useful to distinguish between *toxic-metabolic*, *mechanical*, *vascular* and *infectious causes*. In a small group of patients in whom acute pancreatitis cannot be attributed to any known factors, the condition is described as idiopathic.

The *toxic-metabolic* causes of acute pancreatitis include, beside the excessive consumption of alcohol, specific forms of hyperlipidemia, hypercalcemia, and certain medications. Hyperlipidemia, predominantly in the form of hypertriglyceridemia and hyperchylomicronemia, with mild to moderate elevation of the serum concentrations, is found in almost half the patients with acute pancreatitis. Frequently, these are secondary forms of hyperlipidemia, most often type IV or V of the Frederickson classification; a primary form of hyperlipidemia is rarer. Since hyperlipidemias of type IV or V are often the result of excessive alcohol consumption, the hypertriglyceridemia may only play an aggravating or promoting role. A primary causal role has so far been demonstrated exclusively for the type I form. Due to its content of chylomicrons (milky cloudy plasma), type I hyperlipidemia has an adverse effect on the rheologic properties of blood and this, possibly through ischemia and shock, may lead to acute pancreatitis. Hypercholesterolemia is occasionally combined with hypertriglyceridemia in some patients with acute pancreatitis, but familial hypercholesterolemia itself is not a triggering factor for acute pancreatitis.

Hypercalcemia is a metabolic cause, usually of endocrine origin. This factor, however, is rarely the sole cause of acute pancreatitis; in a large study of patients with primary hyperparathyroidism and hypercalcemia, only 1.5% developed acute pancreatitis. Obviously, additional factors are required before hypercalcemia can trigger acute pancreatitis. One such situation is cardiopulmonary bypass; anesthetic groups that used a large quantity of exogenous intravenous calcium infusions had a higher incidence of 'post-pump' pancreatitis.

Certain medications are an important cause of pancreatitis, although it is often difficult to demonstrate a clear, direct association between individual drugs and acute pancreatitis. Frequently, patients are taking several drugs concurrently and in such cases it is not easy to assess the role of an individual medication. The drugs that are definitely implicated either directly or indirectly (through other mechanisms such as induction of hyperlipidemia) include furosemide, estrogens, azathioprine, valproic acid, *L*-asparaginase, 6-mercaptopurine, methyldopa, sulfonamides, tetracyclines, and pentamidine. Azathioprine induces acute pancreatitis in 1–4% of patients with Crohn's disease and asparaginase in 7% of patients with leukemia. The rate of inducing pancreatitis is substantially lower for all the other medications listed. A new product, DDI (and its analogues), an antiretroviral agent used in the treatment of AIDS, and its analogues may induce acute pancreatitis in up to 20% of treated patients. The proposed mechanisms of the drug-induced triggering of acute pancreatitis differ widely and have not yet been definitely elucidated. In the case of thiazides, for example, a calci-

Etiology

Toxic and metabolic factors

Alcohol
Hypertriglyceridemia (endogenous, exogenous)
Uremia, hypercalcemia (hyperparathyroidism, exogenous)
Scorpion venom (Trinidad)
Drugs
Definitely:
Azathioprine; sulfonamides; furosemide; valproic acid; pentamidine; DDI (antiretroviral agent); tetracyclines; estrogens; *L*-asparaginase; 6-mercaptopurine; methyldopa
Probably:
Chlorthalidone; ethacrynic acid; diazides

Vascular factors

Cardiovascular shock (cardiac surgery)
Polyarteritis nodosa, other immune arteritis syndromes
Atheroembolism
Hypothermia
Malignant hypertension

Mechanical factors

Gallstones
Trauma (blunt abdominal trauma, surgery)
ERCP
Intraductal papillary mucinous neoplasms
Periampullary neoplasms
Duodenal diverticula
Worm infestation (Ascaris, Clonorchis)
Ductal cancer of the pancreas (rare)

Infections

Viruses (mumps, Coxsackie, adenovirus)
Mycoplasma

Idiopathic pancreatitis

Postoperative pancreatitis

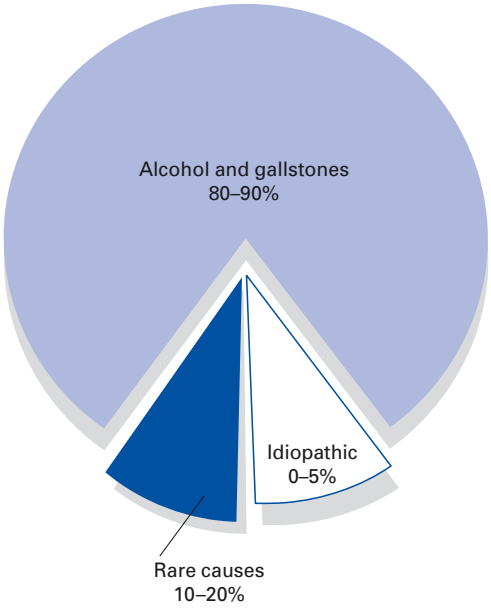
um-mediated effect is thought to be responsible, while for estrogens, acute pancreatitis appears to be induced secondary to the development of hypertriglyceridemia. The role of corticosteroids is highly controversial, and most experts do not believe that corticosteroids are a cause of acute pancreatitis. For individual patients, the recommendation is to withdraw any drug that is a potential cause of acute pancreatitis.

Particular attention should be paid to 'laboratory pancreatitis', i.e. an increase in pancreatic enzymes without associated symptoms. In such patients, it is recommended to withdraw the drugs prescribed without any other clinical/therapeutic measures. In view of the frequent ingestion of over-the-counter preparations, one should be aware of increased enzyme levels occurring in the course of such treatments. A rare form of metabolic cause is acute necrotizing pancreatitis secondary to a specific scorpion sting; this cause has so far been found only in Trinidad.

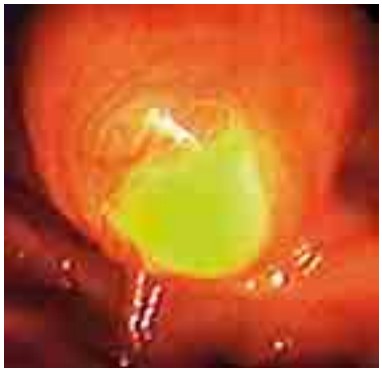
The *mechanical causes* of acute pancreatitis include, besides gallstones, postoperative anatomic changes in the region of the ampulla of Vater or bile ducts, duodenal or direct pancreatitic trauma, obstruction of the pancreatic duct due to neoplasms (or even infestations of worms such as *Ascaris lumbricoides* or *Clonorchis sinensis*), or other rare causes. The postoperative causes include various forms of gastrojejunostomy, in which the afferent limb of the gastrojejunostomy is obstructed (afferent limb syndrome), leading to a marked increase in the intraduodenal pressure which induces reflux of activated, bacterially contaminated digestive juices into the pancreatic duct. Surprisingly, the occurrence of acute pancreatitis as a late effect after endoscopic papillotomies is extremely rare. In contrast, acute manipulation of the papilla in conjunction with injection of contrast media into the pancreatic or bile ducts in the context of ERCP causes acute pancreatitis in 1–3% of patients. In the case of therapeutic procedures at the papilla (e.g. sphincterotomy, stent insertion, biliary manometry), acute pancreatitis can occur in as high as 5–8% of patients but usually with a mild course.

Acute pancreatitis is an unusual manifestation of patients with endoscopic pancreatic ductal cancers arising from the main pancreatic duct. However, in periampullary neoplasms that intermittently obstruct the papilla, acute pancreatitis may occur in 1–3% of such patients as the presenting symptom. Endocrine neoplasms, lymphomas, and pancreatic metastases from other tumors are very unusual causes. One exception is intraductal papillary mucinous neoplasm. This potentially malignant cystic neoplasm arising in the main pancreatic duct often presents with recurrent, low severity, acute relapsing pancreatitis that mimicks chronic pancreatitis. Blunt abdominal trauma (after traffic accidents, a kick from a horse, etc.) often results in acute pancreatitis, not infrequently associated with rupture of the pancreatic duct in the neck of the gland overlying the spine. A developmental anomaly of the pancreas – pancreas divisum – is a highly controversial cause of acute pancreatitis. Pancreas divisum occurs in about 6–10% of all humans and represents an absence of fusion between the ventral and dorsal portions of the gland. Most of the pancreatic juice in this condition is secreted via the minor duodenal papilla into the duodenum. In certain individuals, too narrow an opening in the minor papilla may result in obstruction of ductal

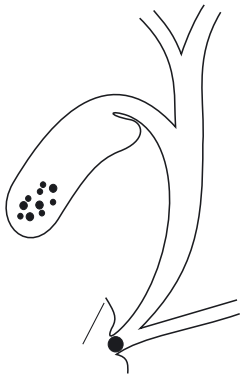
Incidence



Impacted Papillary Stone



Endoscopic view. Prominent papilla with impacted stone.



Stone in the common channel.

drainage. A very small group of such patients with too small an ostium as a result of acquired stenosis of the papilla initially have acute exacerbations which ultimately culminate in the chronic obstructive form of pancreatitis.

Vascular causes of acute pancreatitis include systemic diseases, e.g. arteritis nodosa and various collagen diseases. After cardiac surgery or extensive thoracic surgery, the incidence of acute pancreatitis can be as high as 4–5%. The triggering mechanism in this etiology is believed to be secondary to reduced perfusion with impaired microcirculation or, as mentioned above, secondary to use of calcium infusions for their inotropic or antiarrhythmic effects. Severe hypothermia is also believed to predispose to acute pancreatitis. Together with vasculitis, immunologic factors are also discussed as potentially involved in the development of acute pancreatitis. The mechanism may consist of vascular-mediated impairment of perfusion as well as direct immunologically triggered damage to acinar cells.

A special form of acute pancreatitis is posttransplant pancreatitis, which occurs in the context of a pancreatic organ transplant for the treatment of diabetes mellitus. This form of pancreatitis can present as an early or late form. The early form of transplant pancreatitis is probably a consequence of ischemia and/or reperfusion injury, while the late form may be secondary to a combination of mechanical obstruction of exocrine secretions, immunologic mechanisms, immunosuppressant agents, and viral infections.

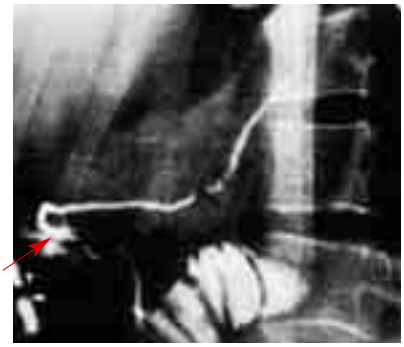
Infectious causes include the mumps virus, Coxsackie virus and Mycoplasma. The causal association with these pathogens appears to be attributable to a rise in antibody titers. In rare instances, acute pancreatitis may also result from diarrheal infections caused by *Campylobacter jejuni* or *Campylobacter coli*, or Salmonella.

A rare cause of pancreatitis is hereditary pancreatitis, which manifests itself clinically as early as the 4th or 5th year of life with acute abdominal pain and quickly progresses with repeated parenchymal injury to chronic pancreatitis. Detailed genetic studies have shown hereditary pancreatitis to be secondary to specific mutations in the trypsin gene. These mutations lead to intracellular activation of the trypsin proenzyme or to muta-tions in intracellular trypsin inhibitors such as SPINK1, which can no longer inhibit prematurely activated intracellular trypsin.

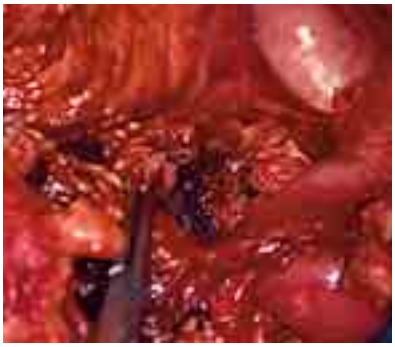
If none of the known causes listed can be identified, the pancreatitis is described as idiopathic. The less the precision taken in excluding all known and confirmed factors, the more often this term will be used; in contrast, as we learn more about the pathogenesis of acute pancreatitis, less episodes will be relegated to the idiopathic variety.

A less well understood form of idiopathic acute pancreatitis is postoperative acute pancreatitis. When this occurs in the setting of aortic surgery, one naturally assumes it to be somehow related to ischemia or an embolic event, but it can also occur without any known predisposing event other than abdominal surgery; this is often a severe form of pancreatitis.

Pancreatic Trauma (Kick from a Horse) with Ruptured Duct



ERP: extravasation of contrast medium at the level of the head of the pancreas (arrow).



Intraoperative findings with localized necrosis.

Worm Infestation

Ascaris lumbricoides, removed from the gallbladder of a patient with acute pancreatitis, also presumably partially obstructing the pancreatic duct.

Pathogenesis and Pathophysiology

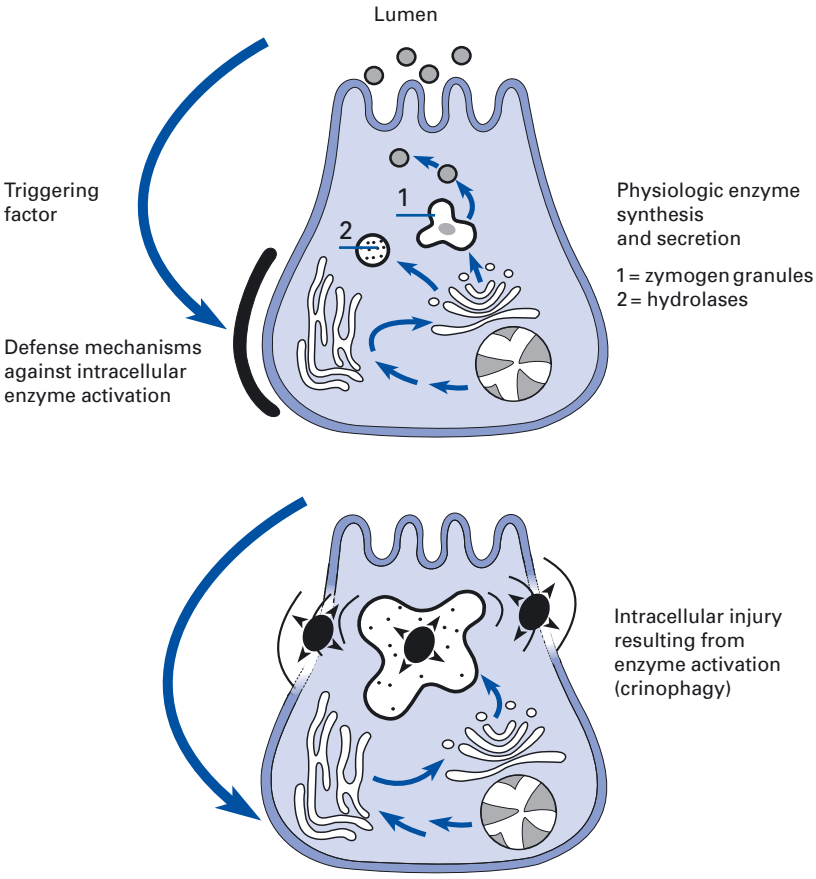
Depending on the causal factor, the pathogenesis of acute pancreatitis develops most probably from direct acinar cell damage, as one would expect, especially with metabolic causes, or possibly via intraductal activation of enzymes and the passage of the latter into the interstitial region of the pancreatic tissue. Through either of these mechanisms, the pathologic process results in morphologic damage. With certain etiologic factors, there may be a combination of impaired intraductal permeability and direct damage to the acinar cells, each potentiating the other. Our knowledge to date of the pathogenesis of acute pancreatitis is almost wholly derived from animal experiments. Acute pancreatitis has been triggered in various diverse models (rat, mouse, opossum, cat, dog) by increasing the pressure in the pancreatic duct in combination with activated pancreatic enzymes or intraductal toxins (bile), with impairment of ductual permeability, via direct acinar cell damage by cellular toxins, or interestingly overstimulation with pancreatic secretagogues (CCK, cerulein).

The mechanism of direct cell damage proceeds via disruption of the normal cell compartmentalization with disruption of intracellular trafficking of zymogen granules. Whereas under physiologic conditions, precursors of the pancreatic enzymes (the inactive proenzymes) are protected against early activation and resultant autodigestion by intracellular protective mechanisms (compartments), this intrinsic intracellular mechanism of protection is disrupted by the specific triggering toxins or secretagogues. This pathologic process results in fusion of the zymogen granules containing the inactive enzyme precursors with the lysosomes (so-called 'colocalization') causing the enzymes to be activated by acid hydrolases within the lysosome and inducing cell death (crinophagy). This process of fusion of the zymogen granules with the lysosomal hydrolases is possibly facilititated by inhibition of secretion (release of enzymes) by the acinar cells due to the inciting factor. A complex system of intracellular and interstitial self-defense mechanisms, consisting of antiproteases (a_1-antitrypsin, a_1-intertrypsin and a_2-macroglobulin), then comes into play to limit the cellular damage caused by the premature enzyme activation. If these protective mechanisms are exhausted locally or are ineffective secondary to genetic mutations (e.g. hereditary pancreatitis), the acute disease process cannot be arrested. Further damage at the systemic level can be ameliorated only if the complex antiprotease system can inactivate the activated enzymes released from the pancreas. An alternate pathogenesis involves activation of the enzymes in the pancreas or surrounding tissues via an intraductally initiated noxious process associated with mechanical disruption of the pancreatic duct. In the interstitial compartment, lipase and phospholipase A_2 are chiefly responsible for initiating the inflammatory process via fatty tissue digestion and necrosis.

Regardless of the site of initiation of the inflammation, there is subsequent activation by numerous enzymes, coagulation factors and inflammatory mediators which determine the damage to different degrees depending on the locally available defense mechanisms within the pancreatic and peripancreatic tissue.

It remains unclear which mechanism causes the interstitial edematous form of acute pancreatitis to progress to the necrotizing form and at

Pathophysiology (Acinar Cells)



Triggering factor	Defense mechanism
Obstruction of intracellular trafficking of zymogens Systemic toxic injury of the acinar cells Changes in cell and tissue compartmentalization (colocalization) Intracellular activation of intrapancreatic enzyme Inhibition of zymogen release from acinar cell	Synthesis of enzymes as inactive zymogens (pro-enzymes) Storage of zymogen granules Inhibitors of protease activity (acinar cells) Serum antiproteases Unimpeded drainage of secretions and lymph Blood perfusion of organs

what time, or whether, after the very first stage, the two entities take separate clinical and pathologic courses. Phospholipase A_2 and elastase appear to have a decisive role in determining the degree of local injury as well as the induction of SIRS.

In view of the predominant roles of primary alcohol and gallstones, an outline is given of the presumed pathogenesis of these two primary forms of acute pancreatitis.

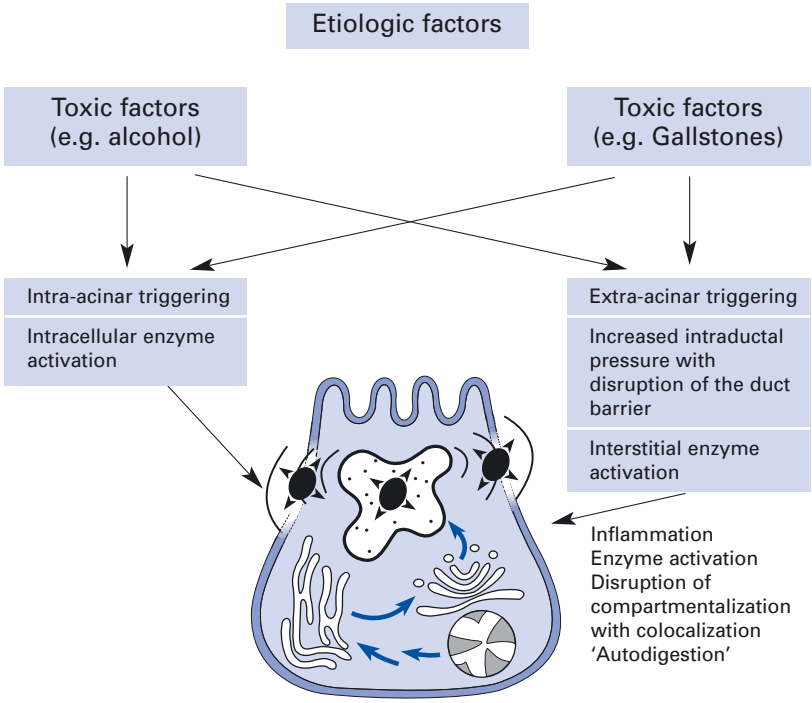
Alcohol-Induced Pancreatitis

In general, the data available to date indicate that alcohol abuse over many years in susceptible individuals results in chronic damage to the pancreas and, in this way, in the presence of existing or ongoing parenchymal injury, initiates an attack of acute pancreatitis. In addition, there are clinical reports of individual patients who develop acute pancreatitis after a binge of alcohol intake. The pathogenesis of injury by alcohol and its metabolites (including acetaldehyde) appears to be mediated by direct cytotoxicity, and leads to the above-mentioned intracellular processes of loss of cell compartmentalization, colocalization, and intracellular activation of enzymes. Another purported mechanism postulated by some investigators involves an effect on the sphincter at the papilla with pathologic reflux of the duodenal contents, increase in duct permeability, and subsequent interstitial activation of pancreatic enzymes. Alcohol abuse stimulates formation of viscous pancreatic secretions rich in calcium and protein which may block enzyme secretion with resultant intracellular enzyme activation. The combined effects of these factors and their relative importance remain controversial.

Gallstone Pancreatitis

The etiology of gallstone pancreatitis was first recognized by Opie in 1901. An autopsy on a patient who died of acute pancreatitis revealed an impacted stone in the ampulla of Vater. Subsequent clinical studies on biliary pancreatitis supported this concept of gallstones as the triggering factor. However, unlike the original case history reported by Opie with an impacted stone, as a rule, in 80–95% of patients, the stones pass the papilla spontaneously. This observation suggests that the cause of the illness is unlikely to be related to a persistent obstruction of bile flow, but rather to transient obstruction with temporary impairment of the sphincter mechanism. Even transient obstruction of the papilla is evidently sufficient to induce pancreatitis. A congenital feature common to about two thirds of humans involves the distal common bile duct joining with the pancreatic duct to form a short (<1 cm) 'common channel' that then enters into the papilla. This common channel was for a long time considered an essential condition for the induction of gallstone pancreatitis. This concept formed the basis of the theory that the bile reflux into the pancreatic duct interfered with intraductal permeability and initiated the inflammatory process in the pancreas. On the basis of a number of experiments on opossums, the increase in pressure in the pancreatic duct and not the reflux of bile into the pancreatic duct is now considered to be the decisive factor in the development of this transient obstruction-induced acute pancreatitis.

Pathogenesis



Local effect	Systemic effect
Edema, Necrosis, Hemorrhage (Pancreas), Ileus, Ascites / pleural effusion, Obstructive jaundice	Organ failure (pulmonary, renal, cardiovascular), Activation of the cascade systems

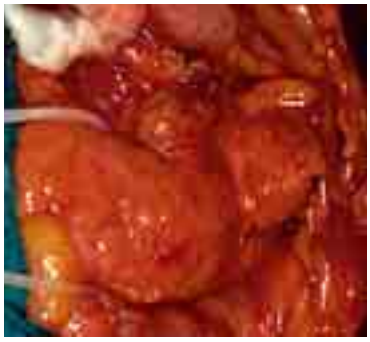
Pathology

The macroscopic and microscopic changes in acute pancreatitis range from mild enlargement of the gland (interstitial edema) to total necrosis of the parenchyma. In anatomic terms, the changes are not just qualitative but increasingly quantitative in severity. This means that clinically mild, interstitial edematous pancreatitis may be associated with a small degree of extrapancreatic fatty necrosis. In contrast, patients with severe acute pancreatitis may present primarily with extrapancreatic necrosis with little or no discernible parenchymal necrosis.

Usually, however, patients with clinically mild pancreatitis will have only edematous swelling of the organ with interstitial fluid accumulation, a very mild leukocytic infiltration of the pancreas (if even present) and few if any areas of patchy parenchymal necrosis. Clinically severe necrotizing pancreatitis, on the other hand, is associated with extensive necrosis of acinar cells in conjunction with substantial interstitial and intravascular infiltration of leukocytes and impaired microcirculation, which histologically is evident as stasis or even thrombosis of intrapancreatic vessels. In the presence of early lesions of acute pancreatitis, changes in the microcirculation lead to ischemia, and cell death which participates in triggering in the pancreas the full syndrome of necrotizing pancreatitis.

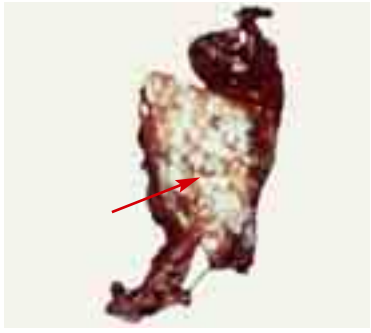
From the clinical viewpoint, the development of necrosis is the most important event in the course of acute pancreatitis, because subsequent complications, whether local or systemic, develop on the basis of the death of pancreatic tissue. These sequelae include infection (infected necrosis and pancreatic abscess), pseudocysts, hemorrhage, and ischemia of the pancreas and adjacent organs. Systemic multi-organ failure results from release of vasoactive substances and activated pancreatic enzymes from the dead tissues into the portal circulation and subsequently into the systemic circulation.

Normal Pancreas



Normal pancreas in situ.

Macroscopic Preparations



Peripheral necrosis with normal parenchyma up to the pancreatic duct (arrow).

Total pancreatic necrosis. Pancreatic duct (arrow).

Histology

Necrotizing pancreatitis. Acinar cell necrosis, extensive leukocytic infiltration.

Clinical Aspects

Mild and severe forms of acute pancreatitis do not differ in their initial clinical manifestations. The primary symptom is significant pain, which as a rule is in the upper abdominal region (epigastric), and can reach dramatic intensity within a brief period. In the majority of patients, the pain spreads like a belt across the upper and middle abdomen and in about half the patients radiates through to the back. In contrast to simple biliary colic, the pain increases still further in the first few hours and rapidly brings the patient to the hospital. The pain syndrome is, however, not pathognomonic to allow acute pancreatitis to be differentiated from other disorders. The primary conditions to be ruled out in the differential diagnosis are acute myocardial infarction, a perforated ulcer, mesenteric infarction, and other inflammatory conditions in the abdominal cavity causing peritonitis. The absence of pain should seriously question the diagnosis of acute pancreatitis; one exception might be marked autonomic neuropathy associated with long-standing diabetes mellitus. In patients in whom the diagnosis is delayed, extrapancreatic complications may predominate with the abdominal pain having largely resolved. In critically ill or obtunded patients in an intensive care setting and mechanically ventilated patients unable to give an appropriate history, severe necrotizing pancreatitis can occur, which is of course masked and may only be diagnosed by a deterioration in cardiovascular parameters or septicemia.

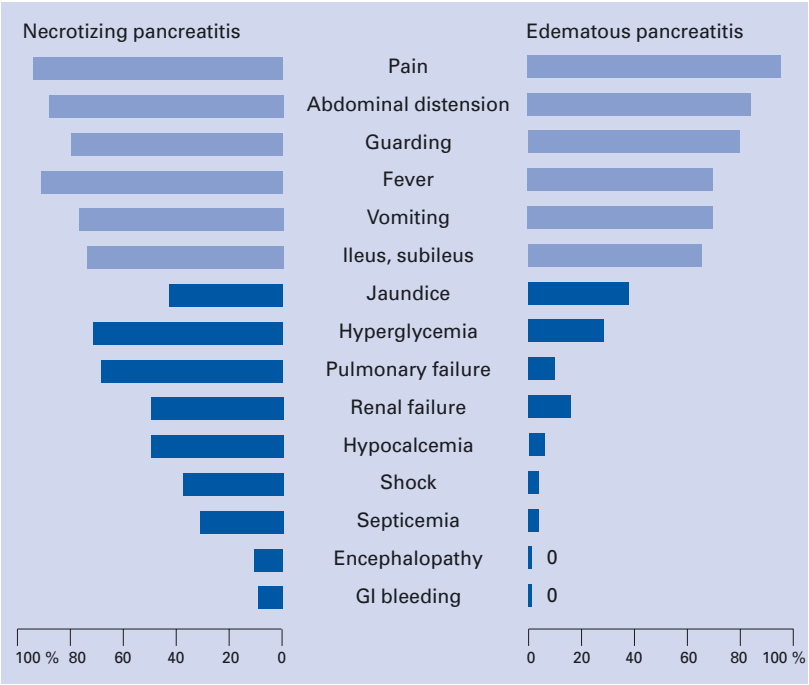
The signs and symptoms most frequently accompanying pain in acute pancreatitis are fever, nausea, vomiting, and adynamic ileus. In this context, it is important to understand that the severity of the pain offers no guide for distinguishing the severity of the pancreatitis, and that fever in the initial stage of acute pancreatitis is not an expression of a bacterial inflammatory process or even of underlying necrotizing pancreatitis but rather of a systemic process and thus does not represent an automatic indication for antibiotic treatment (see 'Treatment').

Clinical Findings

Typically, the patient is agitated, tachycardic, and often looks ill. The abdomen is very sensitive to touch and palpation usually reveals an abdomen with moderate guarding which, however, is distinguishable from the board-like rigidity of classic peritonitis. The tenderness is usually most marked in the upper abdomen, but it may also be diffuse. Some patients have diffuse peritonitis that is indistinguishable from peritonitis of other causes and can closely mimick the physical findings of an intra-abdominal catastrophe.

Only very rarely (<2% of patients with necrotizing pancreatitis) do characteristic cutaneous signs develop due to necrosis of the subcutaneous fatty tissues and bleeding into the abdominal region. The initially bluish-red discoloration of the skin changes over the first 1–2 days to an increasingly pale yellow color; depending on the site, described as Cullen's sign (around the navel), Fox's sign (in the inguinal region) and Grey-Turner's sign if it affects the flank. These signs were originally considered to indicate a poor prognosis but currently represent only a minor aspect of pancreatitis, the outcome of which is determined by extrapancreatic organ failure (lungs, kidneys, cardiovascular system).

Signs and Symptoms



Differential Diagnosis

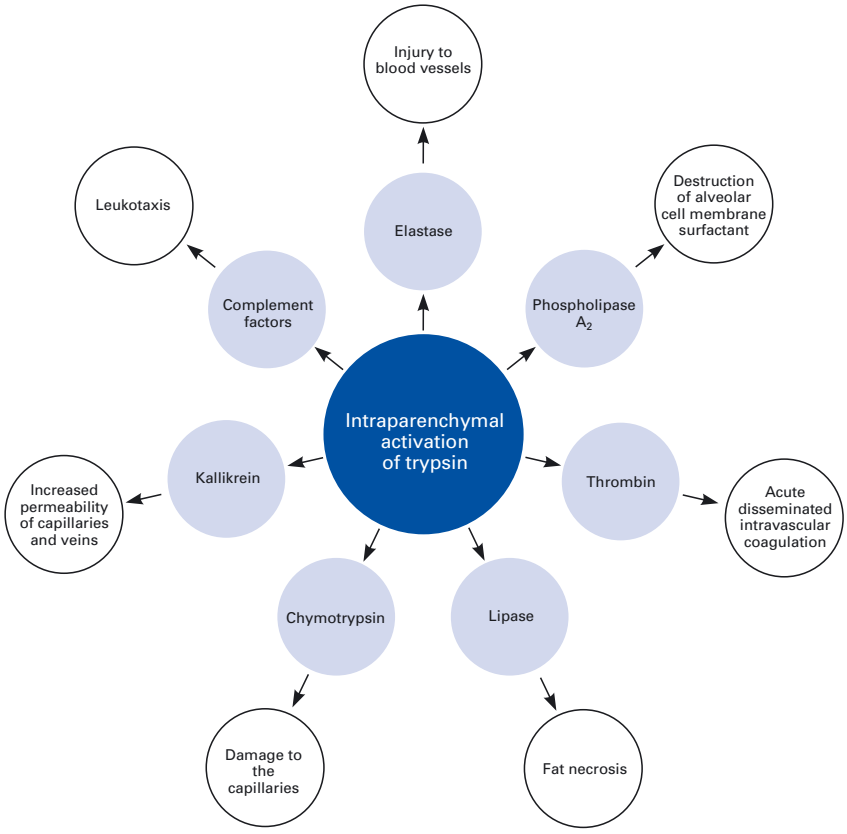
Complications of peptic ulcer
Acute cholecystitis/biliary colic
Intestinal obstruction
Mesenteric infarction
Peritonitis
Colonic diverticulitis/perforation
Pleurisy/pneumonia
Myocardial infarction
Renal colic

Clinical Phases

Local as well as systemic complications may occur during the course of acute pancreatitis. As a rule, such complications are associated with necrotizing pancreatitis, their occurrence being determined in large part by the extent of the necrosis in the pancreatic tissue itself as well as by involvement in the necrotizing process of structures adjacent to the pancreas. Necrosis may become infected in the course of pancreatitis (usually evident by the 2nd or 3rd week) and be the primary factor for the development of serious, potentially life-threatening complications. The natural course of acute necrotizing pancreatitis involves two stages. The first stage is marked by the influx of vasoactive toxic substances, often leading to massive retroperitoneal exudation of fluid (2–10 liters). In individual patients, the release of toxic substances may cause shock, renal failure, and respiratory insufficiency. In the majority of patients, these complications, when appropriately recognized, can be reversed by aggressive resuscitation in an ICU setting.

Infection of the pancreatic and/or peripancreatic necrosis occurs within the first 2–3 weeks, but often has a latent or subclinical period of 2–4 weeks. Infected necrosis develops in 30–40% of patients with severe necrotizing pancreatitis and appears to be decreased to 15–20% by the use of appropriate prophylactic antibiotics. Infections may present as systemic septicemia with multiorgan failure. Infection of the necrosis and the resultant septic complications represent the principal cause of mortality of acute necrotizing pancreatitis.

Enzyme Effects



Clinical Phases of Necrotizing Pancreatitis

Early stage (vasoactive-toxic) ≤ 2 weeks	Late stage (septic) ≥ 2–4 weeks
Mediators: Histamine, trypsin, PLA_2, lipase, activated complement, bradykinins, prostaglandins, etc.	Mediator: Endotoxin
Systemic manifestations: Heart, lungs, kidneys, liver, brain	Septic complications

Complications

Local Complications

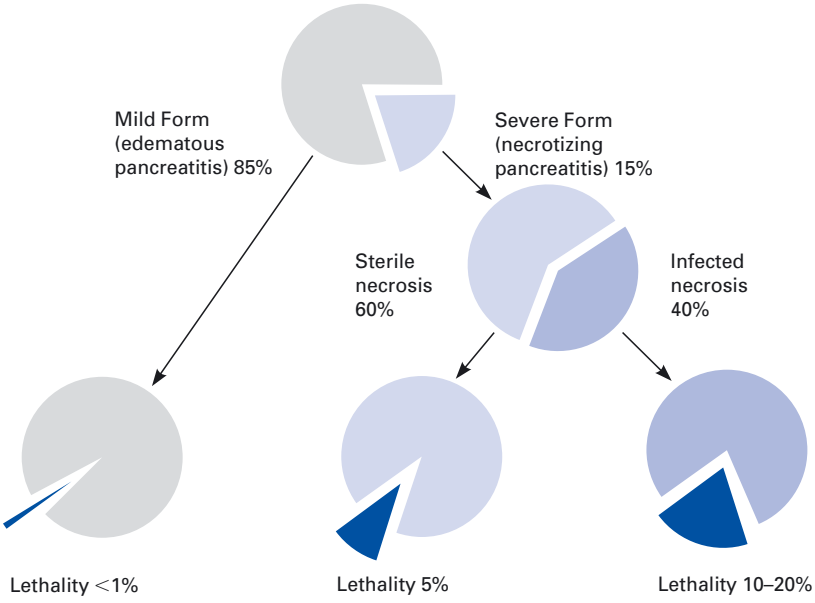
Depending on the severity of the inflammation and the inflammatory response in both the pancreas and the peripancreatic region, a spectrum of complications can arise in the pancreas itself and in the adjacent structures. The most serious complication is necrosis of the pancreatic parenchyma as well as extensive fat necrosis in the peripancreatic retroperitoneum which may extend down to the pelvis and rostrally up to the mediastinum. This necrosis becomes evident clinically over the initial 4 days of the disease, but probably had its origin from the onset of the acute pancreatitis. The necrotizing process may extend to adjacent visceral structures, e.g. the small or large intestine, which in rare cases leads to necrosis and perforation of the bowel.

Between 30 and 70% of patients with severe necrotizing pancreatitis develop infection of the necrosis after the first week. This is a decisive factor in the further course of the disease. Infected pancreatic necrosis may lead to multi-organ failure. In the past, prior to our understanding of the importance of aggressive resuscitation, many patients with severe acute pancreatitis died in the early stage of the disease as a result of shock and resultant organ failure (liver, lung, kidney), due to escape of vasoactive and toxic substances into the systemic circulation. Because of our increasing knowledge of the pathophysiology of the disease and improvements in intensive care, very few patients die during this stage. In contrast, development of infected necrosis and its consequences are currently the primary factors determining mortality. Mortality of patients with infected necrosis is twice that of patients with sterile necrosis (20 versus 10%). Pulmonary, renal or cardiovascular organ failure is also higher in patients with infected necrosis.

There are five possible routes by which bacteria can superinfect pancreatic necrosis: (1) hematogenous infection via circulating blood, (2) reflux into a disrupted pancreatic duct via the duodenum and the major duodenal papilla, (3) reflux of bacterobilia into a disrupted pancreatic duct, (4) translocation via intestinal lymphatics and (5) direct transperitoneal spread. In an animal model of acute pancreatitis, pancreatic infection could be prevented by completely 'sealing off' or isolating the colon from the peritoneal cavity by wrapping it in an impermeant bag; this observation suggests that translocation from the large intestine seems the most likely source of bacteria. Interestingly, spontaneous bacterial translocation into the pancreatic region occurs in health, but does not cause infection and injury in the healthy organ.

The incidence of infection in patients with necrotizing pancreatitis depends both on the duration of the illness and on the extent of the necrosis. The probability of superinfection of necrosis increases from 24% in the first week of the illness to 36% in the second and 71% in the third week. Patients with extensive necrosis are at greater risk than those with focal necrosis. The bacterial spectrum from infected necrosis reflects the intestinal flora with predominantly gram-negative organisms (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus* and *Klebsiella* spp.), but also gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus faecalis* and *Enterococcus*). More recently, the infective spectrum has changed from one of primarily gram-negative bacteria to one of gram-positive cocci and Candida species.

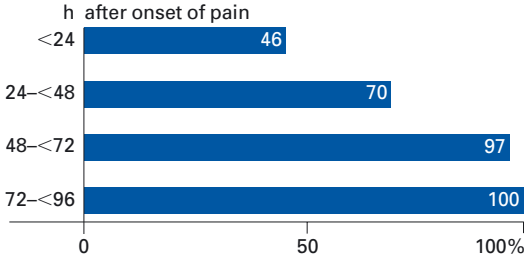
Prognosis



Complications

Local	Systemic
Necrosis	Pulmonary failure
Hemorrhage	Renal failure
Abscess	Shock
Paralytic ileus	Septicemia
Pseudocyst	Encephalopathy
Ascites	Hyperglycemia
Pleural effusion	Hypocalcemia
Jaundice	Metabolic acidosis

Pancreatic Necrosis



Development of pancreatic necrosis. After 96 h, all patients with necrotizing pancreatitis exhibit signs of necrosis (CRP, CT).

In patients who develop infection late into the course of the disease, from the 4th to 6th week onwards, the necrosis tends to be well demarcated with formation of a pancreatic abscess. Necrotizing pancreatitis may cause hemorrhage as a result of inflammatory injury to major vessels with the formation of a pseudoaneurysm which can cause a potentially life-threatening hemorrhage; this complication, in the absence of prior necrosectomy, is exceedingly rare.

About one third of patients with acute pancreatitis develop a pseudocyst, which often resolves within 3 months of the onset of the acute episode. Pseudocysts form either on the basis of inflammatory injury of the pancreatic duct or its branches with exudation of pancreatic secretions, or by the development of a capsule around a fluid exudate or area of necrosis; the latter is not a true pancreatic pseudocyst because it does not communicate with the pancreatic exocrine system and might be better termed an area of liquifaction necrosis. Pseudocysts and other pancreatic fluid collections may develop within and outside the pancreas. Complications of such peripancreatic inflammatory fluid collections result either from compression of visceral structures or the bile duct. In extremely rare cases, hemorrhage into the cyst may result from a pseudoaneurysm or rupture of the cyst.

Paralytic (adynamic) ileus is a frequent complication of necrotizing pancreatitis that appears to develop as a result of extensive retroperitoneal fluid sequestration and the release of vasoactive or inhibitory mediators.

Pancreatic ascites is a rare event which results either from rupture of the pancreatic duct with accumulation of enzyme-rich secretions in the omental bursa and/or free abdominal cavity. Pleural effusions may be unilateral or bilateral and frequently represent a sympathetic response to the intra-abdominal inflammatory process. In rare cases, massive pleural effusion results from rupture of the pancreatic duct with extravasation of exocrine secretions which track into the pleural cavity or from rupture of a pseudocyst into the pleural cavity. These two types of pleural fluid collections can be differentiated by the amylase content of the pleural fluid.

Jaundice is frequently transient and may be caused by temporary or persistent obstruction of the bile duct by a gallstone or by compression of the distal common bile duct secondary to inflammatory swelling of the head of the pancreas.

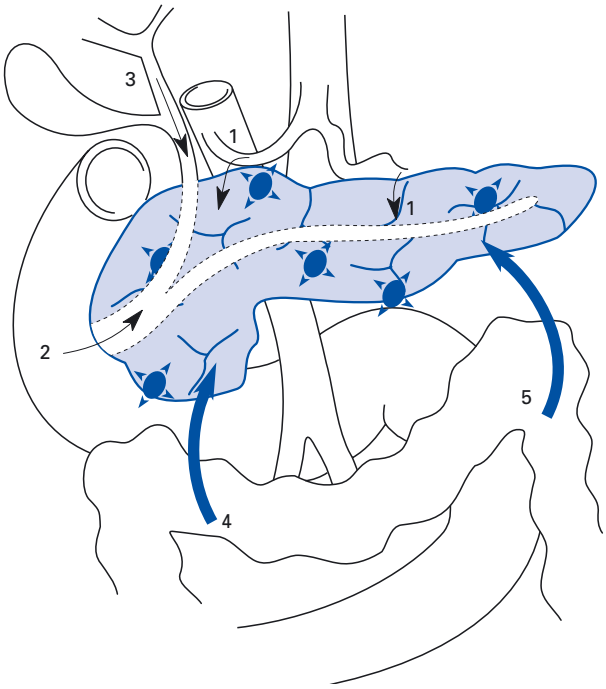
Systemic Complications

Respiratory Complications

Respiratory complications can result from several causes: pleural effusion; atelectasis; pneumonia; mediastinal abscess; and the most severe form, ARDS.

Tachypnea, mild respiratory alkalosis, and low-grade hypoxemia occur frequently in patients with acute pancreatitis, usually in the first 2 days after onset of pancreatitis; however, in the absence of radiographic evidence of morphologic changes in the lung parenchyma, they are not grounds for concern. The milder form of hypoxemia can be controlled easily by pain relief, pulmonary physiotherapy, and administration of supplemental oxygen. Pleural effusions can be treated by pleurocentesis. A critical marker of the severity of acute pancreatitis is a reduction in the pO_2 to <70 mm Hg in patients without prior pulmonary disease. A further reduction in the pO_2 to

Routes of Infection



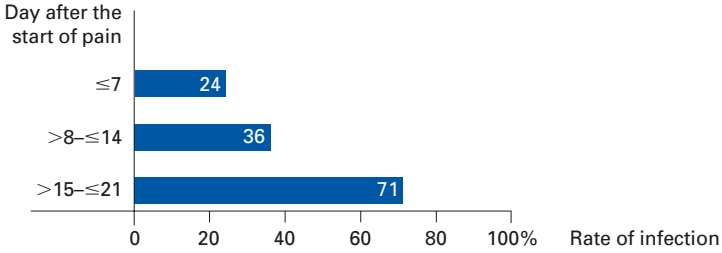
1 = Hematogenous; 2 = reflux of enteric content from the duodenum; 3 = reflux of bacterobilia; 4 = lymphogenous (translocation); 5 = direct transperitoneal spread.

Spectrum of Bacteria and Their Frequencies

Type	Frequency, %
Escherichia coli	26
Pseudomonas spp.	16
Staphylococcus aureus	15[1]
Klebsiella spp.	10
Proteus spp.	10
Streptococcus faecalis	4
Enterobacter spp.	3
Anaerobes	16
Fungi	5–10[1]

[1] The frequency has been increasing recently, possibly secondary to use of broad-spectrum prophylactic antibiotics

Infection Rate in Necrotizing Pancreatitis



<60 mm Hg despite administration of supplemental oxygen is a sign of impending respiratory failure and the potential need for tracheal intubation and mechanical ventilation. The development of ARDS may be diagnosed early in the toxic stage of the disease (first few days after onset of pancreatitis) or delayed until the second week onwards in association with the development of septicemia. In terms of the pathophysiology, local release of active pancreatic enzymes, lysosomal enzymes, as vasoactive substances, and particularly phospholipase A_2 (direct destruction of surfactant) are implicated in the development of ARDS in acute pancreatitis. Histologically, the lungs contain accumulations of PMN leukocytes which, via their release of oxygen free radicals, are responsible for the pulmonary parenchymal injury.

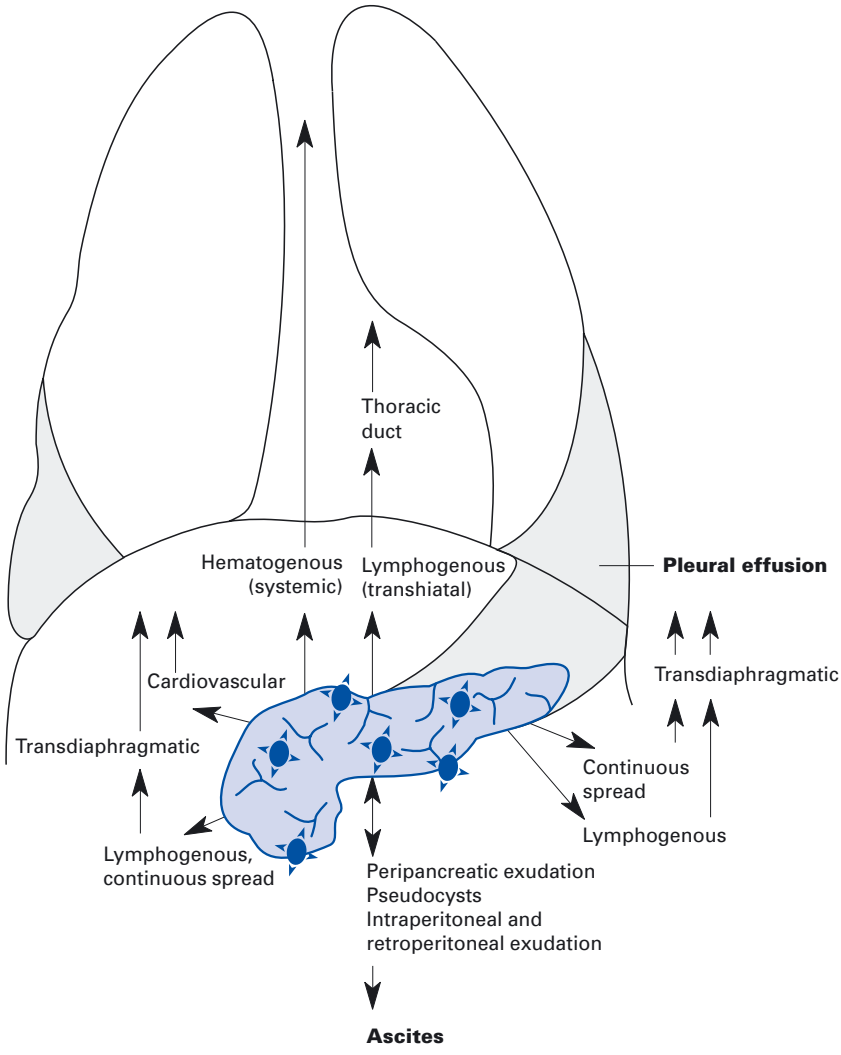
Cardiovascular Complications

These complications include ECG changes, pericardial effusion, hypovolemia and hemodynamic changes. ECG changes are rare and primarily involve cardiac arrhythmias in patients without known preexisting heart disease. ECG changes due to hypocalcemia with prolongation of the QT interval are rare. Pericardial effusions are also unusual and tend to be minimal. Hypovolemia is a predictable occurrence in the initial stages of acute pancreatitis. A reduction in the intravascular volume of up to 30% has been reported in the first 6 h of patients with severe acute pancreatitis. Intravenous administration of fluids should be initiated immediately in acute pancreatitis, and the volume (4 and 10 liters) is best determined by central venous pressure. Most of the fluid loss is third-spacing in the retroperitoneum, but there may also be involvement of the peritoneal cavity (ascites). In addition, part of the fluid sequestration is interstitial fluid accumulation in various organs as a result of the generalized increase in vascular permeability. Further fluid losses may occur secondary to vomiting or nasogastric aspiration.

It is unlikely that acute pancreatitis has a direct effect on cardiac contractility. The original description of a specific myocardial depressant factor has not been confirmed in recent studies. Decreased cardiac performance is more likely attributable to metabolic disturbances or to the release of vasoactive substances.

The circulatory status in necrotizing pancreatitis, especially in the presence of infected necrosis, is characterized by an increased cardiac index and reduced peripheral resistance indicative of the sepsis syndrome.

Causes of Pleural Effusion and Pancreatic Ascites



Renal Complications

Hypovolemia and hypotension are the primary factors in the pathogenesis of renal failure in acute pancreatitis. Activation of the renin-angiotensin system has been described in experimental studies and this also can lead to reduction in local perfusion and glomerular filtration. Release of platelet-activating factor from the pancreas may also play a role in changes in renal blood flow.

Renal tubular dysfunction is a constant feature in acute pancreatitis. Complete renal failure is rare in the edematous form but more common in necrotizing pancreatitis. Hemofiltration and hemodialysis may be important treatments of patients with renal failure complicating acute pancreatitis.

Coagulopathy

Clinically relevant coagulopathy with disseminated intravascular coagulation is extremely rare; indeed there is a tendency to hypercoagulability in the setting of acute pancreatitis. In very rare cases, thrombocytopenic purpura has been reported in conjunction with acute pancreatitis. Vasoactive substances (kallikrein etc.) released in the course of pancreatitis are implicated in this coagulopathy.

Metabolic Complications

The most frequent metabolic disorder is hypocalcemia, which may develop in the first week of the disease. Various mechanisms are believed to be responsible for the hypocalcemia. Sequestration of calcium by saponification in areas of fat necrosis is believed to be the primary cause. Another theory relates to the altered release of calcium-regulating hormones, e.g. calcitonin, parathyroid hormone, and glucagon. Hypomagnesemia has been reported in acute pancreatitis and may, by inhibiting secretion of parathyroid hormone, contribute to the hypocalcemia. Moreover, about half the total circulating calcium is bound to albumin; the hypoalbuminemia of acute pancreatitis is one reason for the falsely low serum calcium concentration. Because of this, whenever possible, ionized calcium should be determined, especially in the severe form of acute pancreatitis, and especially so before treatment with calcium infusions. Hypokalemia may be present and calls for rapid correction.

Hyperlipidemia (usually hypertriglyceridemia) occurs in about half the patients with acute pancreatitis and differs widely in severity. Extremely high triglyceride levels are generally associated with a severe acute pancreatitis. Normally, hyperlipidemia is a transient phenomenon, limit-

Systemic Complications

Lungs

Pleural effusion
Atelectasis
ARDS
Pneumonia
Shock lung

Heart

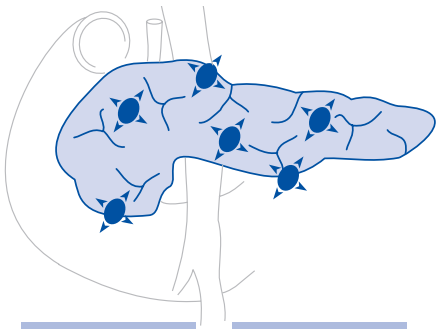
Pericardial effusion
Arrhythmia

Circulation

Hypovolemia
Shock
Hyperdynamic circulation

Brain

Purtscher's disease
Encephalopathy



Metabolic

Hypocalcemia
Hyperglycemia
Hypokalemia
Hypoalbuminemia

Coagulation

Disseminated intravascular coagulation

Kidney

Oliguria
Anuria

Rare

Subcutaneous fat necrosis
Arthritis
Osteolysis
Rhabdomyolysis

ed to the first 2 days, after which the levels rapidly return to normal.

Transient mild hyperglycemia occurs frequently but subsides rapidly without the need for primary treatment. In patients with pre-existing diabetes mellitus, increased blood glucose concentrations can usually be controlled easily by exogenous insulin. In necrotizing pancreatitis, hyperglycemia is a prognostically unfavorable sign as the islets of Langerhans may be involved in the necrotizing process. As many as 40% of patients recovering from severe necrotizing pancreatitis may be left with insulin-dependent diabetes mellitus or some element of glucose intolerance.

Complications Affecting the Central Nervous System

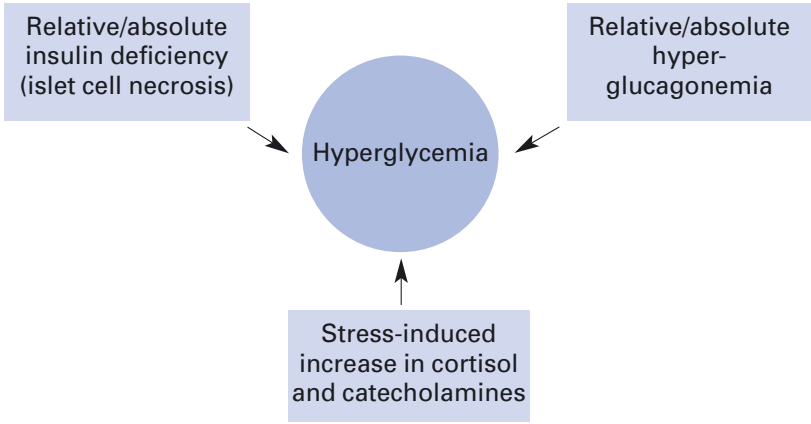
A rare visual disorder, known as Purtscher's angiopathic retinopathy, characterized by visual field defects to the point of total blindness has been associated with acute pancreatitis. Its cause is believed to be an anterior ischemic neuropathy of the optic nerve resulting from an embolism in the end arterioles of the retinal circulation, vasospasm, or leukocyte aggregation (white thrombus formation).

A vague syndrome of pancreatic encephalopathy presents as disorientation, confusion, agitation and hallucinations. It affects primarily patients with alcoholic pancreatitis, but the symptoms may also occur in nonalcoholic pancreatitis. Classic delirium tremens may also complicate the disease in alcoholics and be responsible for the neurologic picture.

Rare Complications

Rare disorders associated with acute pancreatitis include generalized subcutaneous fat necrosis, a poorly understood arthritis, and osteolytic changes in the distal bones. In very rare cases, nontraumatic rhabdomyolysis has been reported in association with acute pancreatitis.

Causes of Hyperglycemia



Autodigestion

Enzyme	Substrate	Effects
Lipase	Triglycerides (intracellular/ intraductal/ peripancreatic)	Fat necrosis Hypocalcemia Local acidosis Intra-acinar lipolysis Cell membrane damage
PLA_2	Cell membranes Phosphatides	Formation of lysophosphatide Membrane destruction Vascular permeability Shock lung, ARDS
Trypsin	Other proenzymes Kallikreinogen Scleroproteins	Coagulation necrosis Shock, vascular permeability Proteolysis, coagulopathy Kinin release
Chymotrypsin/ carboxypeptidase	Scleroproteins	Coagulation necrosis Proteolysis Vascular permeability
Elastase	Scleroproteins Elastic/collagen fibers (blood vessels)	Coagulation necrosis Elastocollagenolysis Proteolysis, vascular permeability, hemorrhage
Kallikrein	Kinins	Kinin release

Diagnosis

The optimal requirements of a diagnostic procedure are the *reliable establishment of the diagnosis* (high sensitivity and high specificity), a suggestion of the *inciting factors*, and – of particular importance – a reliable *prediction of prognosis*.

For the diagnosis of acute pancreatitis, *several laboratory determinations* and *imaging procedures* are available. In conjunction with an appropriate setting and associated clinical findings, an increased plasma amylase activity of >3 times normal allows the diagnosis of 'acute pancreatitis' to be made with a high degree of reliability. A limitation in the use of amylase as a diagnostic marker is that, since it may conceivably arise from extrapancreatic sources (salivary glands, ovaries), it has a low specificity. For instance, in the presence of an atypical clinical picture of acute pancreatitis with respect to characteristics and location of the pain, an increase in total amylase alone cannot be taken as proof of pancreatic injury. The diagnostic specificity has been increased by determination of lipase and pancreatic isoamylase activities. By fractioning of the pancreas-specific and salivary amylases, it is simple to identify the source of the hyperamylasemia. Amylase activity also has certain limitations in its sensitivity. Serum amylase activity may revert to normal levels within several days after the onset of acute pancreatitis. Amylase is cleared rapidly from the blood by renal excretion and serum breakdown. In contrast, lipase is catabolized more slowly, and plasma levels remain increased for longer periods. Thus, lipase is a more sensitive test for acute pancreatitis than amylase when assessed 2 or more days after the onset of presumed acute pancreatitis.

Radioimmunoassays and enzyme immunoassays provide a means of determining serum levels of pancreatic elastase-1 as well as trypsin. These proteolytic enzymes remain increased longer than lipase, only tending to return to normal beginning 8–10 days after onset of disease.

From the practical standpoint, measurement of elastase-1 provides additional information only in selected cases; for instance, severe renal insufficiency, even in the absence of pancreatic injury, is often associated with increased serum amylase and serum lipase (in 20–40% of patients). In contrast, renal insufficiency in the absence of acute pancreatitis is not associated with increased levels of proteolytic enzymes. Determination of elastase, for example, may thus be a highly specific indicator of acute pancreatitis even in the presence of renal failure.

Increased serum amylase and lipase in the absence of any pancreatic pathology may be caused by medications, infectious processes, renal failure or, in the case of amylase only, by disorders of organs other than the pancreas that also produce amylase. Administration of heparin may result in increased lipase levels in some patients. Lipase, too, is synthesized at extrapancreatic sites in the sublingual glands and by the gastric mucosa.

A rare cause of a false-positive increase in plasma amylase levels, macroamylasemia, is due to the binding of this enzyme to immunoglobulins.

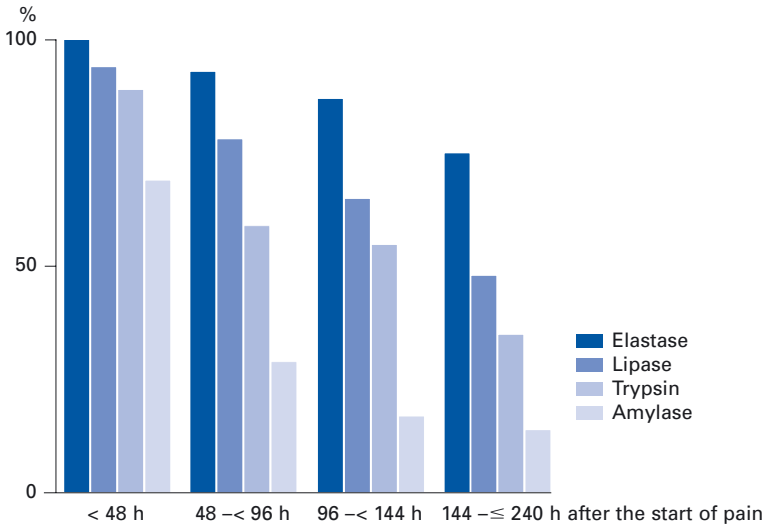
The enzyme concentrations in the serum during an attack of acute pancreatitis do not indicate the degree of damage to the pancreas and are not of prognostic value.

A persistent increase in the serum amylase or lipase after an episode of acute pancreatitis should alert the physician to the possibility of ei-

Causes of Increased Serum Amylase

Pancreas	Pancreatitis	P (= pancreas)
	Pancreatic carcinoma	P
	Obstruction of the pancreatic duct	P
	Trauma	P
	ERCP	P
	Secretin-CCK stimulation	P
Salivary gland	Trauma	S (= saliva)
	Infection	S
	Duct obstruction	S
Renal insufficiency		P + S
Disorders of the gastrointestinal tract	Perforated ulcer	P
	Mesenteric infarction	P
Pulmonary diseases	Pneumonia	S
	Tuberculosis	S
	Carcinoma	S
Neoplasms of the genital organs	Ovaries	S
	Prostate	S
Miscellaneous causes	Macroamylasemia	P
	Diabetic ketoacidosis	S
	Burns	P + S
	Postoperative	P + S

Sensitivities of Different Pancreatic Enzymes for Diagnosis of Pancreatitis



ther pseudocyst formation, including the development of microcysts not immediately evident on ultrasonography or CT, or delayed regression of the interstitial edema. In the absence of symptoms of nausea and vomiting, these laboratory findings should not delay resumption of oral intake.

Acute Biliary Pancreatitis

The identification of a biliary etiology of pancreatitis is based on (1) information from the clinical history, (2) the signs and symptoms, (3) biochemical parameters, (4) gallbladder ultrasonography, and (5) if available, the microscopic examination for microliths or cholesterol crystals in the biliary secretion obtained from the duodenum. The history can provide clues to a biliary cause from previous episodes of biliary colic. The existence of gallstones that had hitherto been asymptomatic should not prevent the search for other potential factors (drugs, previous illnesses), especially in the elderly, because the presence of gallstones may be coincidental and without relevance. The start of the pain in the right upper abdomen radiating to the right shoulder should suggest a biliary cause. Biochemical factors indicative of cholestasis, e.g. serum bilirubin, alkaline phosphatase, γ-GT, AST and ALT may be important. A direct comparison of these liver function tests has shown AST to be the most sensitive for identification of a biliary cause of acute pancreatitis, especially when AST is >60 U/l in the first 12 h after onset of symptoms. After this period, this parameter returns to below the normal cut-off limit.

Transabdominal ultrasonography can demonstrate the presence of gallstones in the gallbladder and at the same time provide information on the presence or absence of common bile duct dilatation.

The combination of ultrasonography with biochemical parameters increases the sensitivity to about 95% and allows the correct determination of a gallstone etiology with almost 100% specificity.

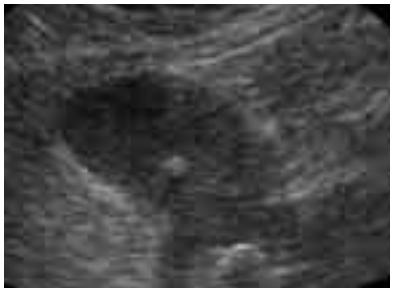
Microscopic examination of aspirated duodenal secretion often allows demonstration of microliths or cholesterol crystals in 'idiopathic' pancreatitis and indicates the likelihood of a biliary cause. This diagnostic test is difficult, uncomfortable for the patient, and not uniformly available and has largely fallen from favor in the routine diagnostic armamentarium.

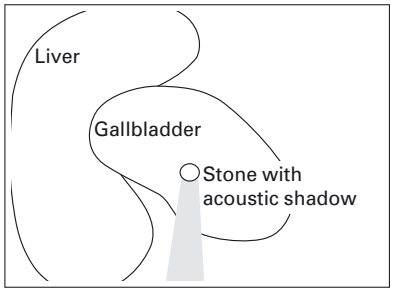
Imaging Procedures

Conventional X-ray examinations (radiographs of abdomen and chest) may suggest the diagnosis of acute pancreatitis by certain effects on the adjacent organs and contribute to the differential diagnosis. Abdominal X-rays can demonstrate calcifications in the pancreas and radioopaque gallstones. In addition, free intra-abdominal air can be excluded as an important distinction from gastrointestinal perforation. At the same time, localized gas within the stomach, duodenum, loops of small intestine (sentinel loop) or the ascending and descending colon (colon cut-off signs) is believed to be related to a localized ileus. Generalized air/fluid levels suggest an associated ileus. Chest X-ray often shows pleural effusions (usually on the left), discoid atelectases, and in more severe pancreatitis, pulmonary infiltrates.

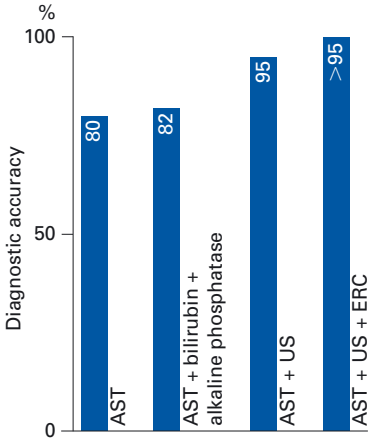
Rapid diagnostic work-up of patients with acute abdominal symptoms usually involves a

Diagnosis of Biliary Pancreatitis





Ultrasonography of cholelithiasis.



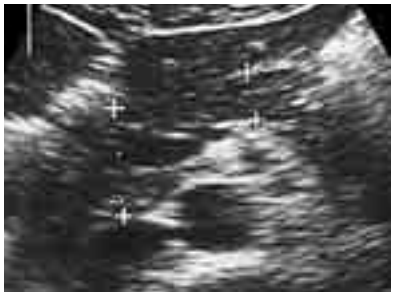
transcutaneous ultrasonography. This noninvasive method may image morphologic changes of the pancreas in acute pancreatitis. This, however, requires an experienced radiologist because there is a limit to the value of ultrasonography in this disorder. Transabdominal ultrasonographic assessment of the pancreas is restricted by the retroperitoneal position of the pancreas (especially in obese patients) and in severe forms of acute pancreatitis by the presence of overlying intestinal gas secondary to the associated ileus. Thus, the sensitivity for the diagnosis of acute pancreatitis, in prospective examinations, is less than 70%, and the ability to recognize necrotizing pancreatitis is about 40%.

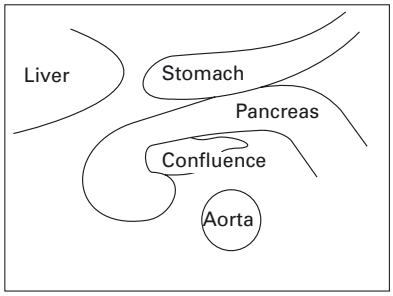
However, the ultrasonographic findings may provide important clues as to the etiology of acute pancreatitis. The presence of gallstones, which may suggest a biliary etiology of the disease, can be demonstrated with virtually 100% accuracy. The presence of small calculi 3–5 mm in diameter is highly suggestive in the absence of another etiology (e.g., alcohol, ERCP, etc.). In contrast, the diagnosis of 'choledocholithiasis' is much less reliable. Whether or not endoscopic ultrasonography (EUS) offers either a more reliable diagnostic test for necrosis or a cost-effective approach is unknown; however, with both its cost and patient discomfort, EUS probably has little to offer except in selected situations.

Ultrasonography has a well-defined role in monitoring the course of patients with acute pancreatitis and, because of the absence of radiation, it may be used and repeated throughout the hospital course. Ultrasonography allows the early recognition of pancreatic or extrapancreatic complications such as ascites, pseudocyst, or abscess formation. Fine-needle aspirations for bacteriologic examination can be repeated under ultrasound guidance of necrosis and fluid accumulations under sterile conditions as a 'bedside' diagnostic technique to search for superinfection (infected necrosis or infected pseudocysts).

CT offers several advantages over ultrasonography. First, it is not subject to examiner expertise. Second, most physicians can better read and understand the CT images. Third, overlying intestinal gas does not prevent imaging of the pancreas. Fourth, the high-density resolution allows visualization of morphologic changes involving the pancreas and the spread of the peripancreatic inflammation to other intra-abdominal and retroperitoneal structures. The sensitivity of CT for diagnosis of acute pancreatitis is about 80%. While this may appear low at a first glance, in mild forms of pancreatitis, the morphologic findings are normal or show only focal changes. CT also offers the possibility of diagnosing necrotizing pancreatitis using the technique of intravenous contrast-enhanced imaging of the presence or ab-

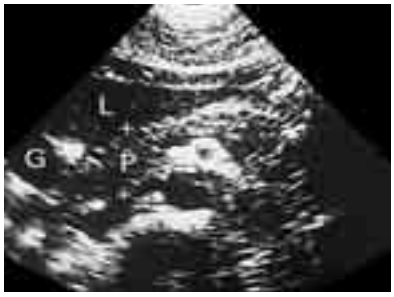
Normal Pancreas

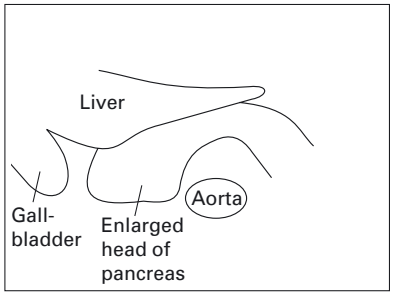




Ultrasonogram showing normal pancreatic parenchyma.
+ = Margins of the pancreas.

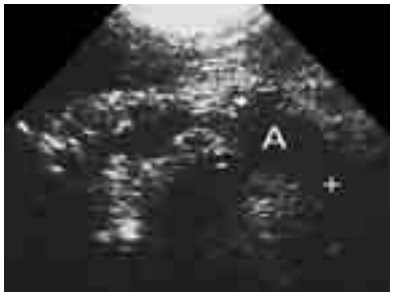
Edematous Pancreatitis

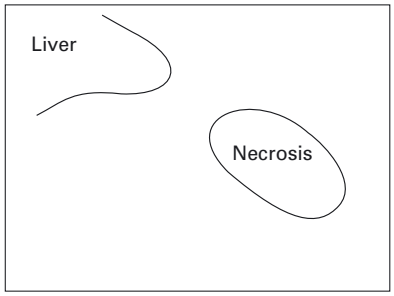




Ultrasonography with edematous swelling of the head of the pancreas.
L = Liver; G = gallbladder; P = edema in the head of the pancreas.

Necrotizing Pancreatitis





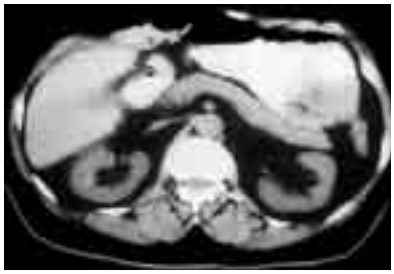
Ultrasonography showing an area of necrosis in the tail of the pancreas.
A = Liquid zone (necrosis) in the tail of the pancreas.

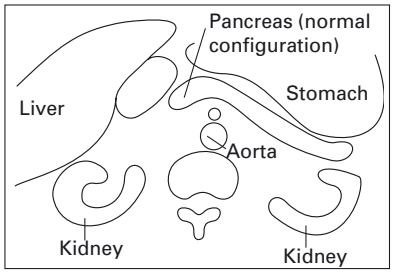
sence of pancreatic parenchymal perfusion. After orogastric administration of a dilute, water-soluble contrast medium, a scan is carried out with a layer thickness of 10 mm prior to giving an intravenous contrast agent. Scans are then repeated with a 5-mm layer thickness after an intravenous bolus of contrast medium. This method offers a high degree of accuracy in the identification of necrosis as perfusion deficits in the pancreas by means of contrast-enhanced scans; the nonenhanced scan cannot distinguish between edema and necrosis. Dynamic, contrast-enhanced CT is now the gold standard for detecting and ruling out pancreatic necrosis, hemorrhage, or extrapancreatic fluid accumulations. Necrotizing pancreatitis can be recognized with 95% accuracy by this imaging procedure. The CT staging proposed by Balthazar into 5 severity ratings has proven useful for routine clinical radiology. It begins with a normal pancreas, progressing to extensive necrotizing pancreatitis: 1. Normal pancreas. 2. Focal or diffuse edematous enlargement of the pancreas (edema). 3. Edema and peripancreatic fluid or inflammatory reaction and fatty tissue infiltration. 4. Focal necrosis of pancreatic parenchyma and peripancreatic fatty tissue reaction suggestive of infected necrosis. 5. Diffuse/extensive necrosis of the pancreatic parenchyma and massive peripancreatic/fatty tissue reaction or objective signs of infected necrosis (gas bubbles in the necrotic lesions).

The disadvantages of CT for diagnostic purposes are that the procedure is both expensive and not universally available and unlike ultrasonography cannot be performed at the bedside. In addition, the safety of CT early in the course of acute necrotizing pancreatitis has been questioned as a result of animal experiments that showed the contrast media to have an adverse effect on the course of acute pancreatitis.These findings were made in a rat model of necrotizing pancreatitis and may be attribued to contrast medium-induced impairment of the microcirculation. Similar adverse effects could not be reproduced in another animal species (opossum) and to date have not been reported in human acute pancreatitis. These observations suggest that CT should only be performed if there are clear indications, such as suspected necrotizing pancreatitis (e.g. increased plasma markers of necrosis) to assess the extent of the necrosis or in the course of the disease to search for the development of complications. Moreover, CT is rarely indicated in the first few days after onset of acute pancreatitis unless the diagnosis is in question and an intraabdominal catastrophe is suspected. Under these circumstances, the information provided by CT far outweighs the theoretic disadvantages.

In the septic patient, a diagnostic fine-needle aspirate with bacteriologic analysis of necrosis or fluid accumulations should be considered concurrently with CT. Fine-needle aspiration under

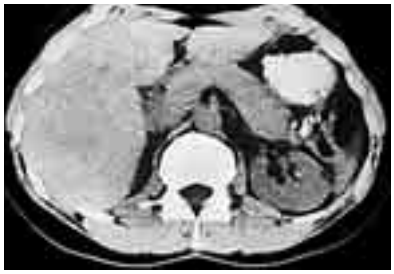
Normal Pancreas

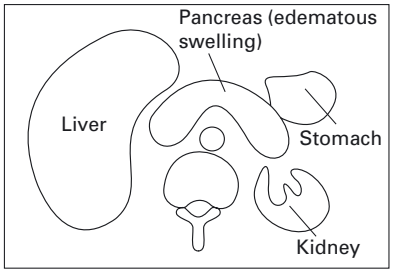




CT: normal view of the organs in the abdomen.

Edematous Pancreatitis

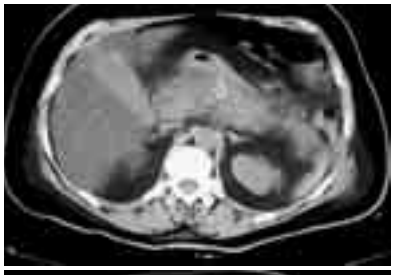


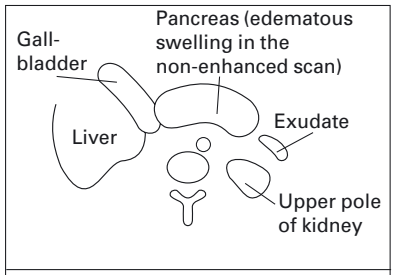


CT: marked homogeneous enlargement of the pancreas in edematous pancreatitis.

Necrotizing Pancreatitis

a





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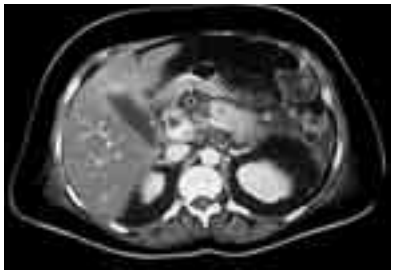
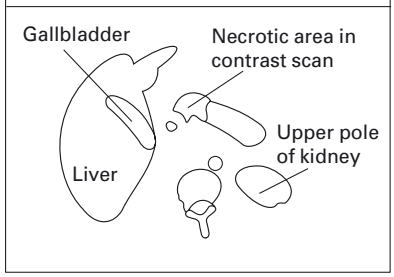


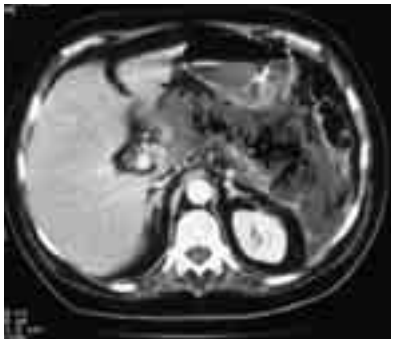


CT: nonenhanced (a) and contrast-enhanced (b) scans. The contrast scan reveals necrotic areas (1) as perfusion defects.

CT guidance is a safe, reliable and risk-free procedure which will identify with a sensitivity approaching 90% whether infection is present or not. In this context, the demonstration of gas in the necrotic areas is pathognomonic of the presence of infection and renders fine needle aspirate unnecessary unless one wishes to delay operative necrosectomy and 'suppress' the systemic effects of pancreatic sepsis with focused intravenous antibiotics in an attempt to delay surgical intervention. CT, however, is indispensable in the planning of a surgical operation and should serve as a road map for the necrosectomy. This imaging procedure allows precise localization of the necrosis and will help to prevent the overlooking of areas of necrosis intraoperatively.

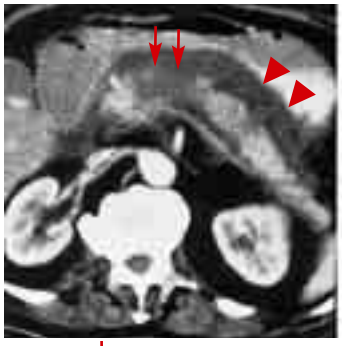
Spiral CT allows optimal resolution of the pancreatic region and enables three-dimensional images to be obtained. Whether the spiral technique offers meaningful and additional information in patients with necrotizing pancreatitis (as opposed to pancreatic cancer) is at the present time not clear. Experience with magnetic resonance imaging (MRI) remains limited. Simultaneous ability to visualize pancreatic morphology, blood vessels and ducts (MRCP) renders MRI of interest for acute pancreatitis. The first studies addressing the comparison with CT confirmed an advantage of MRI in assessing peripancreatic changes, especially detection of fatty tissue necrosis. MRCP which indirectly images the hollow fluid-filled ducts (pancreatic, biliary tree) may make invasive endoscopic visualization of the common bile duct or pancreatic duct unnecessary. A final verdict on the clinical value of spiral CT and MRI remains unsettled at the present time and must be left to further studies.

Infected Pancreatic Necrosis

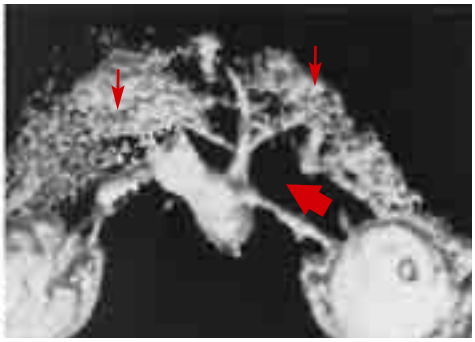


CT showing extraluminal gas in the necrotic areas pathognomonic of infection.

Necrotizing Pancreatitis

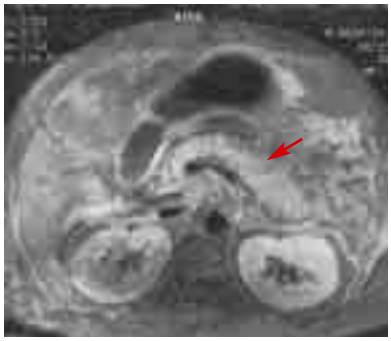


Spiral CT. ↓= Necrotic areas. ▼ = Inflammatory reaction.



Spiral CT, three-dimensional reconstruction. Demonstration of perfused parenchyma (↓) and of necrotic zones (↓).

Edematous Pancreatitis



MRI of edematous pancreatitis (↓).

Prognosis and Classification according to the Degree of Severity

Since the initial clinical presentation provides no immediate indication of the future course of the disease, several multifactorial scoring systems have been developed in the last 25 years that would allow an early prognosis of the future course of the disease. The Ranson criteria, the first classification developed, was based on 11 clinical factors – 5 on admission and 6 others to be evaluated during the first 48 h. Ranson's criteria formed the basis for development of a number of other models of classification/prognosis that utilize various other combinations of clinical and laboratory parameters (Glasgow, APACHE-II, APACHE-III, SAPS). Ultimately they have largely failed to offer markedly improved prognostication.

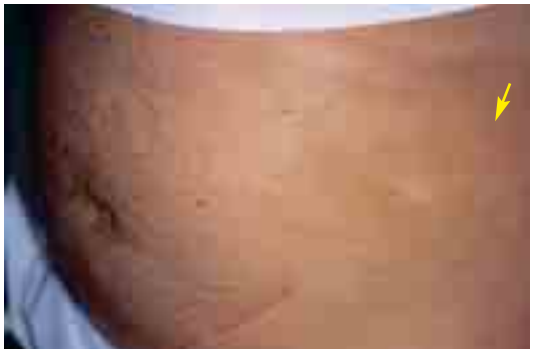
Markers of Necrosis

In parallel with the clinical staging systems, other single prognostic factors were investigated in the blood, urine, and other body fluids. These factors were chosen based on the pathophysiologic cascade of acute pancreatitis. The first parameters investigated were serum ribonuclease, methemalbumin, and the color of pancreatic ascites. However, none of these parameters has found its way into routine clinical practice. An ideal prognostic indicator in the blood or urine should meet the requirements listed in the tables on page 55. Mediators of the systemic inflammatory response syndrome (SIRS) are particularly attractive as potential indicators of severity, and have an important role in the early stages of clinically severe, necrotizing acute pancreatitis. Numerous such parameters have been examined regarding their prognostic validity: acute-phase proteins (e.g. C-reactive protein), antiproteases, complement factors, PMN elastase, trypsin activation peptides, interleukins/chemokines, adhesion molecules, procalcitonin, G-CSF and many others. In meta-analyses and randomized controlled studies, PMN elastase, interleukins, and CRP have as good an accuracy in detecting pancreatic necrosis as contrast-enhanced CT.

C-Reactive Protein

CRP, first described in the serum of patients with pneumonia in 1930 by Tillet and Francis, is an acute-phase protein synthesized in the liver that fulfils numerous functions in the defense against infections (as well as other noninfective specific and nonspecific functions). Mayer and McMahon in 1984 drew attention to the importance of CRP for the differentiation of mild and severe acute pancreatitis. The results of their pilot study have been confirmed in many other studies in the last 20 years. Consequently, CRP currently represents the gold standard among markers of necrosis in the diagnosis of acute pancreatitis in many centers, especially in Europe. CRP can be measured relatively simply and rapidly (laser nephelometry). This fact, as well as its high prognostic validity, with a sensitivity and specificity of 85% at threshold values between 120 and 170 mg/l (depending on the test used) make CRP a valuable parameter in the monitoring of patients with acute pancreatitis. It is important to acknowledge, however, that the maximum accuracy of CRP is not reached until 3–4 days after the onset of acute pancreatitis so that CRP is not an ideal marker of necrosis. However, patients with the disease tend to be transferred to a tertiary hospital with a delay of one or two days, and thus this disadvantage may not be so important clinically in treating these patients definitively.

Grey-Turner Sign



Red-blue discoloration of the flanks.

Ranson Criteria

Findings on admission	Within 48 h
Age > 55 years	Fall in hematocrit by 10%
Leukocytes > 16×10^9/l	Creatinine > 250 μmol/l
Blood sugar > 200 mg/dl	Calcium < 2 mmol/l
LDH > 250 U/l	Arterial pO_2 < 60 mm Hg
AST > 60 U/l	Base deficit > −4 mEq/l
	Extravascular volume accumulation > 6 liters

Hematologic Parameters

Markers of severe acute pancreatitis	
Methemalbumin	C-reactive protein
Ribonuclease	Procalcitonin
α-Antitrypsin	Serum amyloid A
α_2-Macroglobulin	Interleukins: IL-6, -8, -10
Complement factors	TNF-α
Phospholipase A_2 activity	Adhesion molecules
PMN elastase	Endotoxin

Cytokines

A major role of systemic cytokines is induction of synthesis of acute-phase proteins in the liver. The increase in serum CRP concentration in acute pancreatitis is a consequence of hepatocyte stimulation by released cytokines; this explains the delayed increase in CRP in acute pancreatitis compared with the earlier increase in IL-6. The peak of serum IL-6 levels occurs 48–72 h before the CRP increases. With the aid of the interleukins (IL-6, IL-8), it is possible to achieve good differentiation between the mild and severe forms of acute pancreatitis, but these markers are expensive and difficult to assay; therefore they have not so far become established in the clinical arena.

PMN Elastase

The systematic inflammatory response plays an important role in the natural history of acute pancreatitis. One of the first consequences after the onset of acute pancreatitis is migration of inflammatory cells, e.g. the polymorphonuclear leukocytes and macrophages, into the pancreatic parenchyma. Polymorphonuclear (PMN) elastase is the best studied of the substances released by polymorphonuclear granulocytes. In several studies, serum concentrations of PMN elastase correlated with the severity of acute pancreatitis. The increase in serum PMN elastase also occurs before the increase in serum CRP. The prognostic validity of PMN elastase, however, has not proved superior to that of CRP.

Newer Markers of Necrosis: PLA_2, TAP, PCT and CAPAP

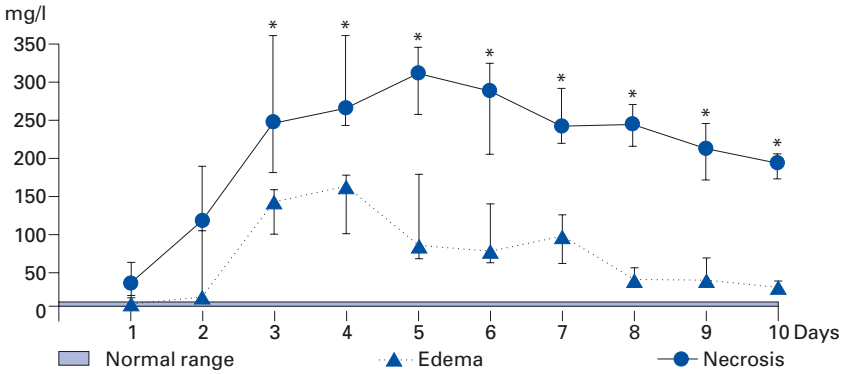
Phospholipases play a critical role in the pathogenesis of acute pancreatitis, not only in the development of intrapancreatic and extrapancreatic necrosis but also in the systemic organ complications of SIRS. Two different types of PLA_2 can be distinguished in the serum of patients with acute pancreatitis: PLA_2 type I, a pancreatic digestive enzyme, and type II, a nonpancreatic secretory PLA_2, the source of which has not yet been identified. Potential sources of these pivotal enzymes are inflammatory cells or the liver itself (acute-phase protein?). Recent studies have shown that type I PLA_2 does not reliably differentiate between mild and severe acute pancreatitis, whereas with type II PLA_2, a correlation has been found with pulmonary failure (destruction of surfactant). A major limitation of type II PLA_2 for routine clinical use as a prognostic indicator of severity of acute pancreatitis is that a routine assay is not available for this isoenzyme.

Trypsinogen-activating peptide (TAP) is a part of the trypsinogen molecule. TAP consists of 5 amino acids, and is released when trypsinogen is activated. In contrast to plasma trypsin, TAP is not bound to protease inhibitors but is rapidly excreted in the urine. The initial results of TAP in predicting the severity of acute pancreatitis appeared excellent, however these results have not been reproduced in all subsequent studies.

Procalcitonin (PCT) was able to distinguish well between SIRS and bacterial sepsis in patients in an ICU setting. Although little is known regarding its source, PCT appeared to provide a significant differentiation between mild and severe courses in the initial stages of acute pancreatitis. Because PCT appeared to be a 'sepsis marker', the initial hope was that it would reliably detect infected pancreatic necrosis, the prime determinant of mortality. An initial study showed PCT to be

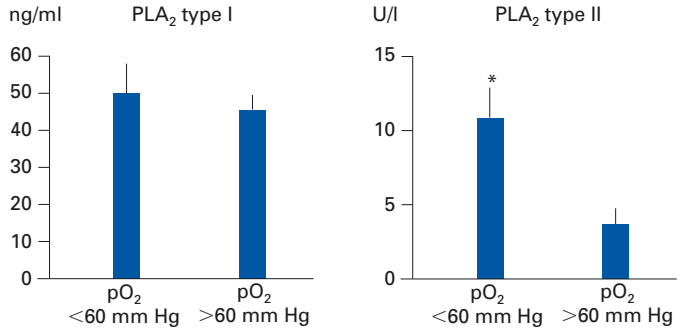
Requirements of an ideal prognostic indicator of severe acute pancreatitis
Objective Reproducible Simple assay methodology Available at all times (emergency laboratory) High validity on admission Unaffected by concomitant disorders Low cost

Change in CRP after Pain Onset



Change in the serum CRP concentration over time (medians and quartiles) in patients with edematous and necrotizing acute pancreatitis.

Phospholipase A_2

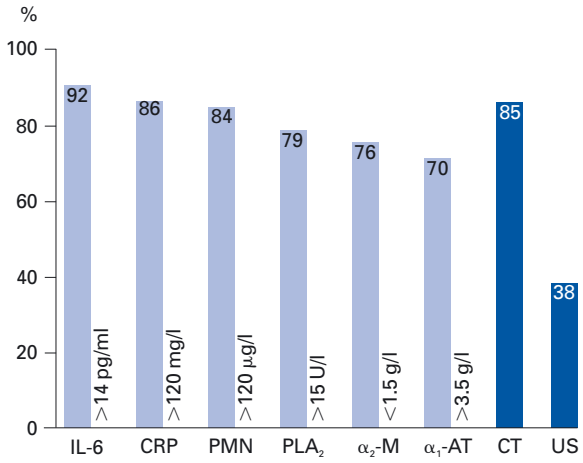


Phospholipase A_2 and pulmonary insufficiency.
Type I = Pancreatic PLA_2. Type II = nonpancreatic PLA_2. *Significant difference.

highly effective in this regard, but this finding was not confirmed in a larger study that evaluated the maximum values obtained during the course of the disease.

Considerable interest remains in a parameter that simultaneously makes the diagnosis and provides prognostic information in acute pancreatitis, as is the case for instance with creatine kinase or troponin in myocardial infarction. For these purposes, a test strip would offer a considerable advantage, such as is used, for instance, to determine blood sugar. However, clinical studies of acute pancreatitis have shown that the absolute increase in serum pancreas-derived enzymes is of no help in the assessment of the severity of pancreatitis. Time will tell whether the more recently introduced parameters will be of clinical relevance, i.e. human pancreas-specific protein (hPASP), carboxylester hydrolase (CEH) and the activation peptide of carboxypeptidase B (CAPAP).

Accuracy of Markers of Necrosis, CT and Ultrasonography



Temporal peaks after onset of disease and validity ratings of the best markers of necrotizing pancreatitis		
	Peaks	Clinical validity
CRP	3–4 days	+++ after 48 h
IL-6	24 h	++ at 24–48 h
IL-8	12–24 h	+++ <24–72 h
PMN elastase	12–24 h	+ at 24–48 h

Treatment

Every patient with acute pancreatitis should be admitted to the hospital because the clinical course can deteriorate rapidly. Moreover pain is difficult to control with oral medications alone.

It is essential to differentiate between mild (edematous) and severe (necrotizing) pancreatitis so that appropriate treatment can be initiated. Patients with interstitial edematous pancreatitis merely require observation, intravenous fluids, and analgesia, while those with the necrotizing form need aggressive resuscitation in an intensive care unit.

All patients with acute pancreatitis, including those with the necrotizing form, should initially be treated conservatively; surgical intervention, which is used almost exclusively in infected necrosis, should not be entertained until, at the earliest, the end of the first week of illness.

Basic Conservative Treatment

The primary treatment of acute pancreatitis is symptomatic support. Any attempts at specific treatment according to the etiology have so far failed. Such treatments have included protease inhibitors (e.g. aprotinin, gabexate mesylate) or regimens with hormones or agents known to inhibit pancreatic secretion. Therefore we treat the symptoms, i.e. pain and when necessary the failure of those organs affected by the acute pancreatitis. Fluid loss is replaced and, when possible, the cause of the pancreatitis eliminated, e.g. the early removal of choledocholithiasis or the somewhat later removal of the gallbladder in patients with cholelithiasis after the pain has resolved.

The basis of this conservative treatment of acute pancreatitis is keeping the patient NPO. This approach is usually maintained for up to 3 days (in relatively mild cases). Nasogastric intubation to evacuate the stomach is essential in severe acute pancreatitis and provides some symptomatic relief for the patient; it may also help ameliorate the associated ileus. A nasogastric tube is not required in mild cases of acute pancreatitis with no signs of nausea or no episodes of vomiting.

Acute pancreatitis primarily affects and involves the retroperitoneum; peripancreatic and retroperitoneal sequestration of fluids (third-spacing) (edema) occurs regularly. As a result, the patient may lose between 2 and 10 liters of fluid which has to be replaced. Adequate and aggressive fluid replacement is thus a critical principle in acute pancreatitis. A central venous catheter should be considered (internal jugular or subclavian vein) to measure CVP. Initially, under CVP control, 3–6 liters of fluid are replaced per 24 h. After 2–4 days, this amount is reduced to a mean volume of 3 liters/24 h. Crystalloid solutions are recommended, but in rare cases, plasma expanders may be necessary. Anemia with a hemoglobin of <9 g/dl should be treated with transfusion.

Parenteral nutrition is not required in mild acute pancreatitis because recovery of gut function and resolution of pain usually occurs by 4 days after onset of the disease. The diet should then be advanced rapidly to a regular diet. In severe pancreatitis, parenteral nutrition should be initiated early (within the first 72 h). A combination of glucose, amino acids (up to 10% solutions) and 10–20% lipid emulsions should be used; electrolyte concentrations can be adjusted to the patient's needs. Only in exceptional cases with marked hypertriglyceridemia is it advisable to omit high-concentration glucose solutions and

Basic Therapy

Obligatory	Optional
Hospitalization NPO Monitoring of blood pressure, pulse and temperature Central venous catheter Bladder catheter for urinary monitoring Intravenous fluids controlled by CVP (>3 liters daily) Analgesia (patient controlled intravenous narcotic) Parenteral nutrition → enteral nutrition	Nasogastric intubation Prophylaxis against stress ulcers Epidural analgesia Antibiotics

Specific Therapy

	Clinical effect
Protease inhibitors:	
Aprotinin (Trasylol®)	not established
Gabexate mesylate (Foy®)	not established
Hormones/inhibitors of pancreatic secretion:	
Glucagon	not established
Calcitonin	not established
Atropine	not established
Somatostatin	not established
Octreotide (Sandostatin®)	not established
Others:	
PAF-antagonist (Lexipafant®)	not established

lipid emulsions. The recommended calorie intake is 30–40 kcal/kg/day with 1.5 g/kg of protein. In severe cases likely to require a longer duration of intensive care, a rapid progression to enteral feeding using a nasojejunal tube has proven both possible and effective; indeed, many investigators believe that enteral feeding helps to maintain the gut mucosal barrier and may even decrease infective complications of the pancreatitis.

The foremost consideration of symptomatic treatment is pain relief. Effective analgesia is best provided by intravenous patient-controlled analgesia (PCA) using morphine, meperidine, or fentanyl. Experience has shown this to provide complete pain relief in at least 80% of patients. Alternatively, opioids may be given by intramuscular or subcutaneous injection. There is no contraindication to morphine agonists. The theoretical risk of spasm of the sphincter of Oddi has never proven clinically.

Surveillance

The term 'surveillance' implies that patients with acute pancreatitis require thorough and regular examination.

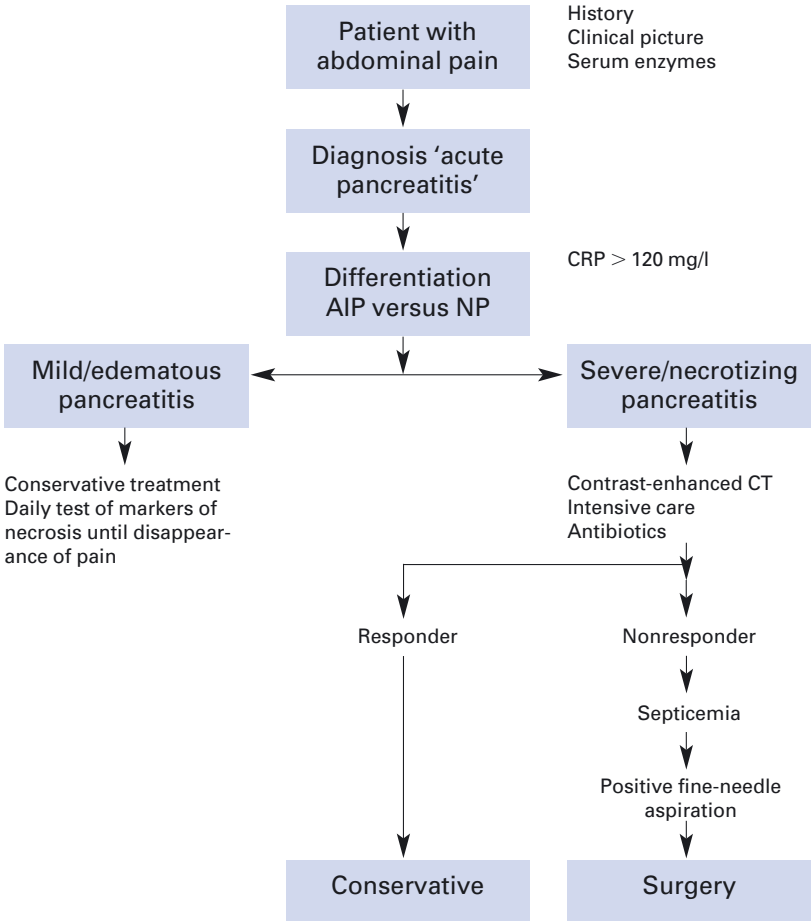
In principle, patients with severe (necrotizing) pancreatitis should be admitted to an ICU while patients with mild acute pancreatitis can be treated adequately in a regular patient ward.

Daily monitoring includes a clinical examination of the abdomen and chest as well as a general clinical assessment of the state of consciousness. Regular monitoring of heart rate, temperature, blood pressure, oxygen saturation and urinary output is required in all patients. For patients with mild acute pancreatitis, such monitoring should be carried out for at least 48 h; for those with severe acute pancreatitis, it should continue until clinical recovery (on average not less than 5–10 days). Laboratory parameters to be determined daily include blood count with hemoglobin, serum amylase, AST, creatinine, blood sugar, and electrolytes (sodium, potassium, calcium), together with a blood gas analysis (pO_2, pCO_2, pH and base excess). Some groups follow serum CRP, since this allows differentiation between mild pancreatitis marker (levels >120 mg/l). These laboratory parameters should be monitored daily in patients with necrotizing pancreatitis, while in patients with mild pancreatitis, it is sufficient to follow these levels for the first 3 days and then again at the time of discharge.

Radiologic examinations (abdominal and chest radiographs, ultrasonography, and CT or MRI) are used selectively. Transabdominal ultrasonography is carried out on admission to hospital and if necrotizing pancreatitis is suspected (CRP >120 mg/l) a contrast-enhanced CT should be carried out after a week or so. If the condition deteriorates, a contrast-enhanced CT should be obtained to look for a cause of the worsening of the clinical course (infection, severe peripancreatic fluid collections, hemorrhage, etc.). Fine-needle aspiration should be used if there is any suspicion of infection. CTs with fine-needle aspiration can be repeated often up to once per week.

X-ray examinations of the abdomen are obtained only if indicated (obstruction). MRI has not become standard practice in acute pancreatitis, but because it has no radiation, it is likely to play a role in the future. The 'all-in-one' MRI gives a more accurate indication of the size of peripancreatic necrosis as well as simultaneous visualization of the bile ducts (MRCP) to identi-

Diagnosis and Treatment of Acute Pancreatitis



Laboratory Monitoring

Leukocytes	Substances excreted in the urine (creatinine, urea)
Hemoglobin (hematocrit)	Alkaline phosphatase
Platelet count	γ-GT
Coagulation parameters (Prothrombin time-INR, PTT)	Bilirubin
Blood gas analysis (pO_2, pCO_2, BE)	AST
Serum electrolytes (K, Na, Ca)	CRP

fy calculi in the common bile duct, thereby possibly preventing the need for ERCP.

If the etiology of acute pancreatitis is not clear, it may be advisable, before the patient is discharged from hospital, either to perform a laparoscopic cholecystectomy (if the etiology is likely of biliary origin) or to carry out ERCP with visualization of the pancreatic duct. This approach eliminates rare causes of acute pancreatitis, such as stenosis of the pancreatic duct or a periampullary tumor with obstruction of the pancreatic duct.

Intensive Care Therapy in Patients with Severe Acute (Necrotizing) Pancreatitis

Patients with severe acute pancreatitis should be treated in an ICU setting. Severe acute pancreatitis is suspected on the basis of the initial examination and initial prognostic scoring (APACHE-II, Ranson/Glasgow criteria), but particularly in the presence of organ failure (kidneys, lungs, cardiovascular system, liver, or metabolism) and, when utilized, an increase in CRP to >120 mg/l.

The diagnosis of 'severe acute pancreatitis' can be confirmed by contrast-enhanced CT, which demonstrates the necrotic process in or outside the pancreas, but CT is usually not necessary for the diagnosis within the first 5 days of onset of the disease.

In addition to the basic conservative therapeutic measures outlined above, preventive and/or therapeutic measures are now possible in an attempt to prevent or ameliorate multi-organ failure and most importantly superinfection of necrosis, the crucial prognostic factor.

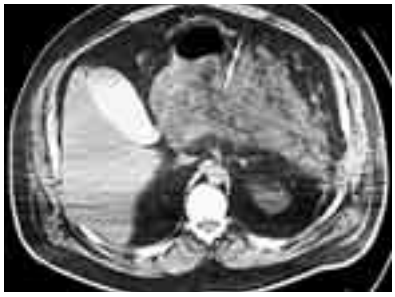
Most pancreatologists believe strongly that patients with necrotizing pancreatitis should be treated with high-dose parenteral prophylactic antibiotics designed to suppress bacteremia and systemic dissemination of bacteria entering the lymphatics, peritoneal fluid, or blood stream. Every patient is potentially at risk of superinfection of the necrotic lesions, thus the aim should be prevention by early antibiotic therapy designed to suppress those organisms most often associated with pancreatic sepsis (gram-negative organisms of gut origin). Also, the antibiotic chosen should be one known to attain high concentrations within the pancreatic parenchyma. Any suspicion of infected necrosis (septicemia, progressive multiorgan failure) should initiate consideration of an ultrasonographic or CT-guided fine-needle aspiration of the necrosis of peripancreatic exudate with gram staining of the aspirate and bacteriologic culture. If micro-organisms are confirmed, surgery will be indicated.

Multi-organ failure in patients with severe acute pancreatitis most often presents as pulmonary insufficiency, and later as renal insufficiency, circulatory failure, liver failure, and metabolic dysfunction.

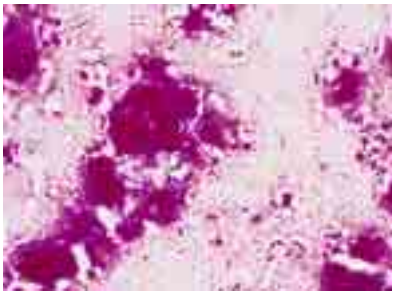
Pulmonary insufficiency is first treated by administration of supplemental oxygen via a nasal tube or face mask. If this fails to raise the arterial pO_2 above 60 mm Hg (blood gas analysis), mechanical ventilation is indicated to prevent local and systemic injury from ongoing hypoxia.

Renal failure as a rule has two components: (1) hypovolemia (prerenal failure) and (2) a direct toxic damage because of mediators of acute pancreatitis. Renal failure manifests as oliguria or anuria and as increased serum levels of sub-

Detection of Infection



CT-guided fine-needle aspiration.



Gram stain with evidence of bacteria.

Intensive Care

Organ complications	Laboratory values	Measures
Pulmonary failure	$pO_2 < 60$ mm Hg $pO_2 < 60$ mm Hg despite supplemental oxygen	Nasal or mask O_2 Mechanical ventilation
Renal failure	Creatinine > 120 μmol/l Urinary volume < 30 ml/h BUN > 30 mmol/l or creatinine > 400 μmol/l	Dopamine (renal dose) + diuretics Hemofiltration Hemodialysis
Cardiocirculatory dysfunction Shock	CVP decreased Mean arterial pressure < 70 mm Hg Systolic blood pressure < 80 mm Hg > 15 min	Volume replacement dopamine (high-dose) norepinephrine or other inotropic agent (Swan-Ganz catheter)
Metabolic disorders	Hyperglycemia >150 mg/dl Hypocalcemia Disseminated intravascular coagulation Metabolic acidosis	Insulin None as a rule Fresh frozen plasma Sodium bicarbonate
Sepsis	Rectal temperature > 38.5 °C Leukocytes < 4 or > 12×10^9/l Platelets < 100×10^9/l Metabolic acidosis Base excess > – 4 mmol/l	Antibiotics Surgical intervention in case of positive fine-needle aspiration
Biliary pancreatitis	ERC/ERCP or mRCP	Papillotomy when an impacted stone is found
Infected necrosis	Fine-needle aspiration	If evidence of infection, surgery

stances excreted in the urine (creatinine, urea). Renal failure should be treated aggressively by adequate fluid administration (crystalloid solutions of up to 10 liters/24 h) using the CVP as a guide. If there is significant associated pulmonary disease, a Swan-Ganz catheter may be necessary. The second step may include use of diuretics (furosemide 20–200 mg/24 h) and the infusion of dopamine to increase renal blood flow (so-called 'renal doses' of 4 μg/kg/min). Further deterioration of the renal failure with increases in the serum creatinine is an indication for continuous hemofiltration and/or hemodialysis in an ICU.

Shock or cardiocirculatory failure requires prompt, aggressive volume replacement, but may also require administration of inotropic agents (catecholamines, α-agonists, etc.) depending on the hemodynamic parameters. One important consideration is often to increase the vascular tone given the reduced peripheral resistance caused by SIRS. One approach is to initially use norepinephrine to augment tone and blood pressure (dose 0.05–0.2 μg/kg/min) and secondarily epinephrine for concurrent support of cardiac output (0.05–0.2 g/kg/min).

Metabolic dysfunction/dysregulation must also be treated in the context of intensive care standards. Coagulopathy may require fresh plasma preparations, hyperglycemia, is controlled with insulin, and metabolic acidosis may necessitate sodium bicarbonate (100 mEq/24 h).

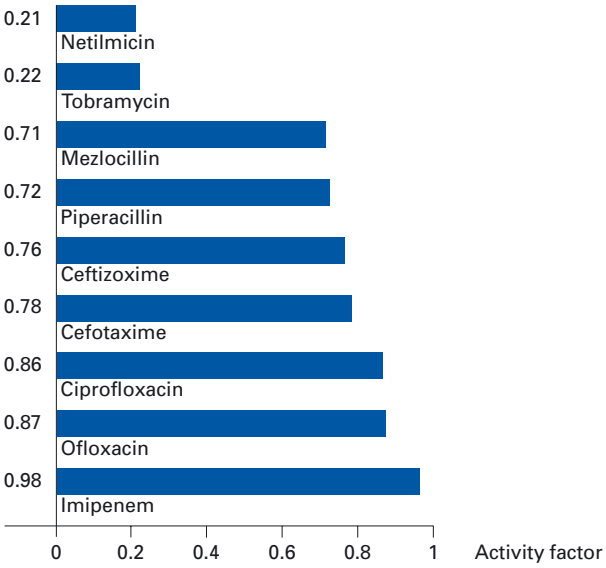
Role of the Infection: Prophylactic Antibiotic Therapy

Patients with mild (interstitial edematous) acute pancreatitis, 85% of the total population of patients with acute pancreatitis, do not benefit from antibiotic therapy. Even if the temperature increases above 38.5°C, which occurs in 80–90% of patients with acute pancreatitis, antibiotics are not needed. Antibiotic therapy is, however, indicated if necrosis is suspected or confirmed on CT. Patients with necrotizing pancreatitis have a 20–40% risk of superinfection in the retroperitoneum. This high risk of superinfection from a source other than the sterile pancreas thus calls for early aggressive institution of antibiotic treatment as soon as the diagnosis of necrotizing pancreatitis is made or suspected. With the use of early antibiotic therapy, it is possible to reduce the incidence of the late complications of necrotizing pancreatitis due to sepsis. The effectiveness of early and adequate antibiotic treatment has been confirmed in several randomized clinical studies and a systematic meta-analysis.

The choice of antibiotic is dictated by the spectrum of pathogens isolated from infected pancreatic necrosis, which, as a rule, consists of gram-negative intestinal and anaerobic microorganisms; an equally important concept is the ability of the antibiotic to penetrate the necrosis. Selective uptake of different classes of antibiotics has been demonstrated in the pancreas as across the blood-brain barrier. Aminoglycosides, for instance, do not adequately pass the blood-pancreas barrier although they would be ideally suited for the expected microorganisms. The recommended treatments are either combinations of a quinoline (ciprofloxacin, ofloxacin) with metronidazole or, alternatively, monotherapy with imipranem/cilastatin. The latter is more commonly used.

The antibiotic therapy should be continued for at least 2 weeks. If improvement in the clinical condition of the patient continues, no further

Activities of Antibiotics



Pharmacokinetic studies on concentrations in the human pancreas.

Antibiotic Treatment in Necrotizing Pancreatitis

Medication	Patients	Infected necrosis,%	Mortality,%
Imipenem/cilastatin	74	12 vs. 30[1]	7 vs. 12
Cefuroxime	60	30 vs. 40	3 vs. 23[1]
Ceftazidime+amikacin + metronidazole	23	0 vs. 58[1]	9 vs. 25
Ofloxacin + Metronidazole	26	61 vs. 53	0 vs. 15
Pefloxacin vs. imipenem/cilastatin	60	34 vs. 10[1]	24 vs. 10
Selective intestinal decontamination[2]	102	18 vs. 38[1]	22 vs. 35

[1] Significant differences versus controls.
[2] Cefotaxime intravenously and orally: colistin sulfate + amphotericin + norfloxacin.

Results of antibiotic therapy in necrotizing pancreatitis from 6 randomized controlled clinical studies.

diagnostic or therapeutic measures are required and consideration for stopping the antibiotic should be entertained. If the patient with necrotizing pancreatitis remains critical despite antibiotic therapy, one should strongly consider weekly fine-needle aspirations, under image control, of the necrosis or the peripancreatic exudate for identification of the pathogen(s). Infected necrosis is an indication for active intervention. Adequate prophylactic treatment with antibiotics, however, does cause a shift in the microbial spectrum and favors gram-positive bacteria *(Staphylococcus aureus)*, fungi and – albeit rarely – multiresistant microorganisms, a very real concern (especially in the relevant areas with endemic MRSA, MRSE, VRE).

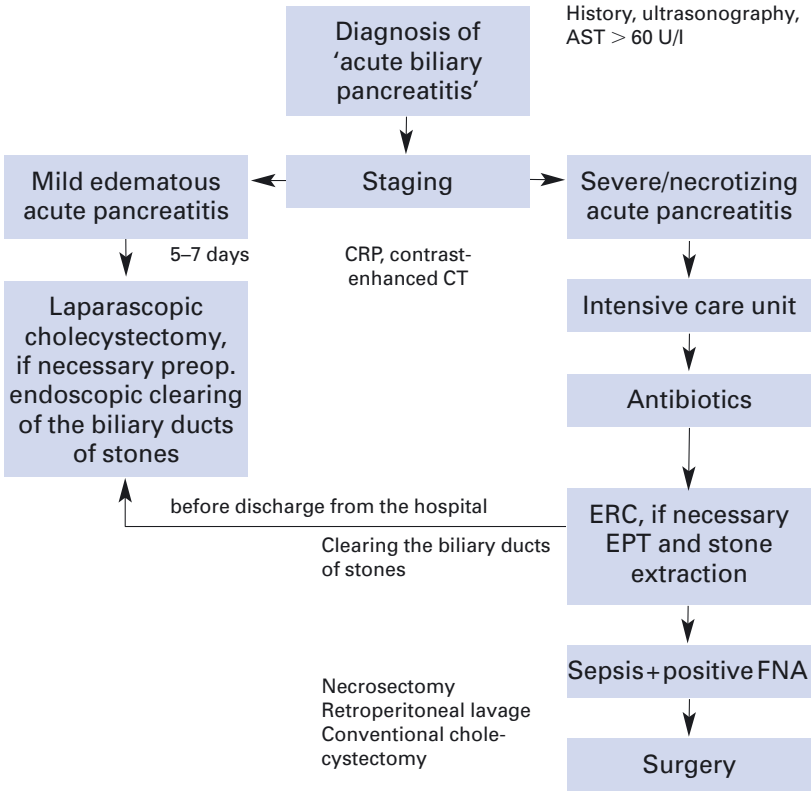
Role of Endoscopic Treatment

If in patients with acute biliary pancreatitis there is reason to suspect an impacted papillary stone (cholestasis, jaundice and/or cholangitis), an ERC or possibly MRCP should be performed within 24 h. This approach allows identification and endoscopic removal (after sphincterotomy) of the biliary calculi in 90% of patients. The endoscopist should be warned against simultaneous visualization of the pancreatic duct because of the risk of microbial contamination; ductal disruptions are common in severe (necrotizing) pancreatitis, and escape of the nonsterile contrast medium into the interstitium can superinfect otherwise sterile necrosis. It has been shown that patients with severe acute (necrotizing) pancreatitis with choledocholithiasis are the ones who benefit from early papillotomy and stone extraction. Patients with alcohol-induced pancreatitis should not be treated with ERC or sphincterotomy.

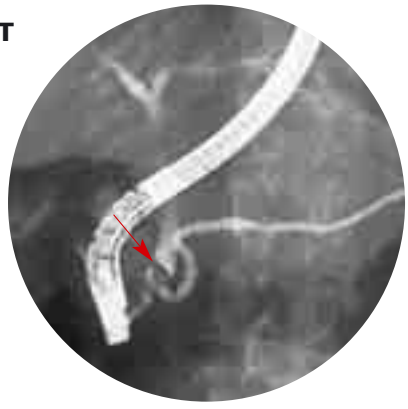
Indication for Surgery in Acute Pancreatitis

Surgical procedures in acute pancreatitis are undertaken based on a selective approach governed by the clinical situation. Some type of surgical intervention is clearly indicated in infected necrosis, generally diagnosed with the aid of fine-needle aspiration and identification of the offending microorganism(s). Necrotizing pancreatitis alone – even if there is extensive pancreatic necrosis – does not in and of itself constitute an indication for surgery. With modern methods of intensive care, patients with sterile necrosis usually do not require surgery. Pancreatic and/or peripancreatic necrosis generally become infected after the first week of illness. The incidence of recognized infection is highest in the third week, i.e. patients with necrotizing pancreatitis are most likely to develop or manifest signs of infection in the third week of illness. In the late course of severe acute pancreatitis, some other potential indications for surgery should be considered, besides infected pancreatic necrosis: interventional (percutaneous) drainage of inadequately treated pancreatic abscesses; symptomatic pancreatic pseudocysts (hemorrhage, space-occupying lesions impinging on stomach, bile duct, duodenum, or portal venous system) and ischemia of hollow organs adjacent to the pancreas (transverse colon) resulting in peritonitis. In rare situations, surgery is necessary because of acute hemorrhage associated with the necrotizing process or when an abdominal compartment syndrome occurs (intraperitoneal pressures, measured by bladder pressure, exceeding 20–25 mm Hg associated with renal and pulmonary failure); this compartment syndrome usually occurs in the first

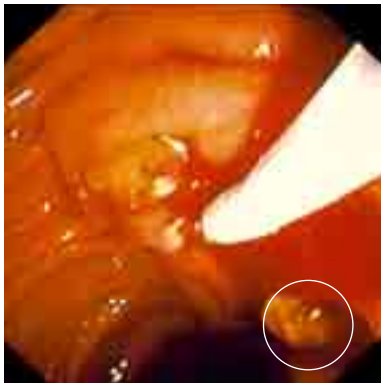
Diagnosis and Treatment of Acute Biliary Pancreatitis



ERC, EPT



ERC visualization of stone (arrow) in common bile duct.



EPT and stone extraction; ◯ = stone.

week of disease onset and only requires abdominal decompression.

The Role of Interventional Radiologic Techniques

In recent years, radiologic diagnostic techniques have given rise to development of percutaneous interventional therapy, a new mode of treatment in the form of drainage systems placed percutaneously under guidance by an imaging procedure (ultrasonography, CT). Approximately 5% of patients with necrotizing pancreatitis develop an isolated, contained abscess in the late stage of the illness (4–6 weeks), i.e. a pus-filled cavity in or near the pancreas as a consequence of the necrotizing process with little or no associated other necrosis. If CT reveals such an abscess with solid walls, interventional percutaneous drainage may be the sole form of treatment. In this highly selected situation, i.e. without associated necrosis or other areas of infected necrosis, the treatment is almost always successful. Even large (>6 cm) space-occupying pseudocysts that cause symptoms may be treated interventionally, especially if the patient's general condition is poor. This approach, even if not definitive, frequently gains time and may be followed up by definitive surgery (cystojejunostomy) if needed.

It is not advisable to use radiologic interventional methods as primary treatment of infected necrosis with diffuse spread in the bed of the pancreas or the retroperitoneal space; radiologic intervention provides drainage and not necrosectomy.

Surgical Procedures in the Treatment of Necrotizing Pancreatitis

The most important concept in surgical treatment of necrotizing pancreatitis is the careful removal of all necrotic areas (necrosectomy) while preserving all viable pancreatic tissue, avoidance of blood loss, and avoiding adverse effects on neighboring structures to prevent iatrogenic surgical complications. Surgical treatment in severe acute pancreatitis is complex, fraught with potential life-threatening complications, and should be left to experienced surgeons. Due to the characteristic disease process and the dynamics of the ongoing necrotizing process in the bed of the pancreas and retroperitoneal space, infected pancreatic necrosis cannot usually be treated by just one (single) operation. It is thus useful to combine the primary operation with an additional treatment approach. One proven method is continuous postoperative closed lavage of the bed of the pancreas and retroperitoneal necrotic tracts after the initial operative necrosectomy. The ongoing mechanical irrigation ensures continuous 'debridement' and evacuation of necrotic material, toxic matter, infected detritus, and extravasated pancreatic exocrine secretions. Continuous lesser sac lavage is continued postoperatively for 2–6 weeks. The volume used ranges initially from 20 to 50 liters/24 h, the lavage fluids should be the standard solutions used for continuous peritoneal dialysis. These solutions are slightly hyperosmolar and thus also evacuate systemic fluid, further providing an element of renal support. The lavage is reduced according to the clinical state of the patient, i.e. if after surgical treatment and intensive lavage, the patients recover from multi-organ failure within 3–8 days, and their condition is stable

Indications for Surgery

Infected pancreatic necrosis	± Positive demonstration of pathogens (FNA, with gram stain and culture) ± Gas bubbles revealed by CT/MRI + Sepsis
Persistent necrotizing pancreatitis	+ >4 weeks of intensive care + no significant clinical improvement

Last Resort in Exceptional Cases

Fulminant necrotizing pancreatitis	+ Rapidly progressive multi-organ failure despite maximum intensive treatment (last resort)

Surgical Procedures

With clinically confirmed success	Without clinically confirmed success
Necrosectomy with closed retroperitoneal lavage **Necrosectomy with wide peripancreatic drainage** **Necrosectomy with staged re-exploration** **Necrosectomy with open packing**	Pancreatic resection Peritoneal dialysis Debridement with sump drainage Interventional drainage

No Resections

Surgical preparation after blind resection.

Necrosis often peripheral.

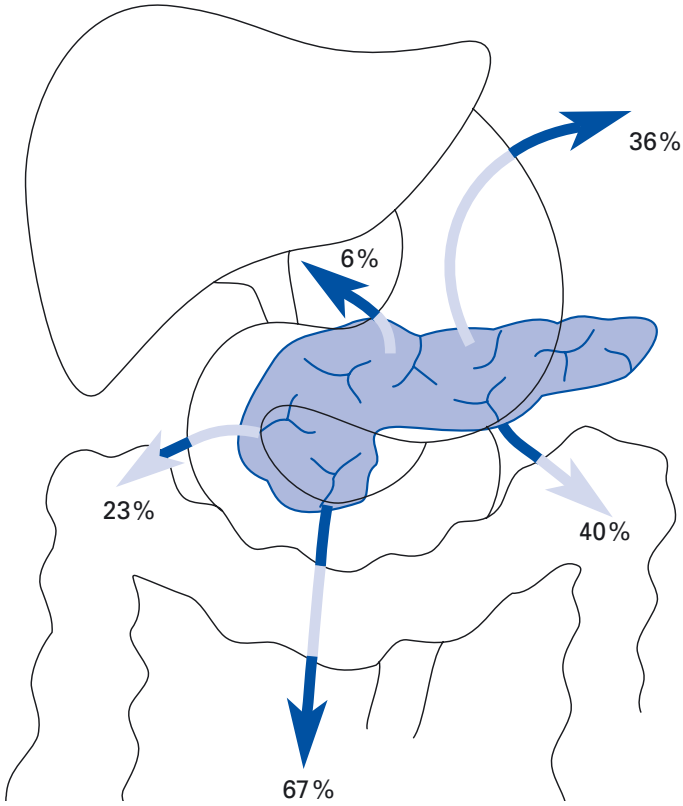
(extubation, cessation of hemofiltration, reduction in catecholamines, normalization of body temperature), the lavage should be reduced weekly and terminated by the third postoperative week. The recovered fluid should be analyzed weekly for amylase or lipase concentrations and bacterial contamination, and inspected macroscopically for necrotic material.

By using this approach of operative necrosectomy in combination with continuous postoperative lavage, the mortality of patients with necrotizing pancreatitis has been reduced to 10–20%.

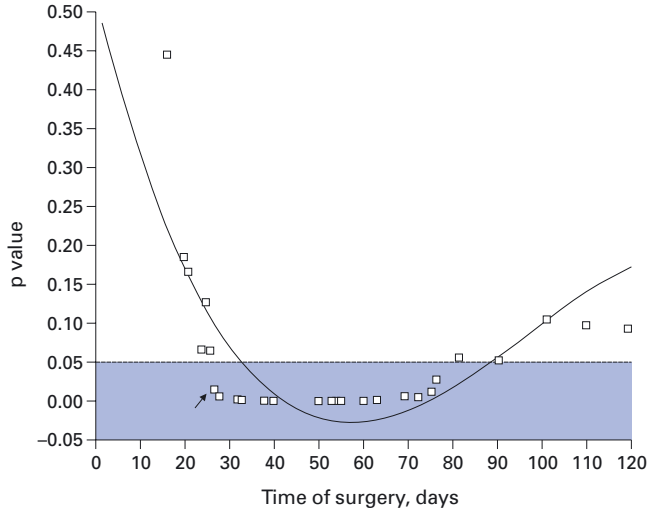
Alternative operative approaches are 3-fold: first, extensive necrosectomy with wide transcutaneous peripancreatic drainage, second the open abdomen or peritoneostomy (open packing), and third planned repeat laparotomy. The latter two surgical modalities are especially appropriate in early interventions before the necrosis is better established and demarcated. Both methods involve treatment of the open abdomen with daily or every other day cleansing of the bed of the pancreas and retroperitoneal necrotic cavities. Due to the frequent surgical interventions, these alternative methods are believed by some investigators to lead to a higher rate of complications, but in experienced hands their long-term results are good and similar to those obtained with closed lavage.

Minimally invasive or laparoscopic procedures may, with the appropriate experience in these techniques, be used for removal of clearly demarcated necrosis in the late stage of the disease; however, patient selection is critical and this approach should be used for patients with relatively localized, established necrosis.

Necrotic Tracts



Time of Surgery



Survival as a function of time of surgery.

Late Results after the Treatment of Acute Pancreatitis

Full recovery is achieved in most patients with acute interstitial edematous pancreatitis; however, treatment thereafter requires eliminating the triggering factors, such as gallstones or alcohol abuse. By contrast, half the patients recovering from necrotizing pancreatitis are likely to be left with some element of endocrine and exocrine deficiency causing diabetes mellitus and maldigestion.

Surgical Treatment of Cholelithiasis

Patients with acute biliary pancreatitis should not be discharged from hospital before undergoing cholecystectomy. The risk of a further attack of acute pancreatitis is markedly increased if the gallbladder is left in place. The incidence of recurrent acute pancreatitis quoted in the literature may be as high as 25–60%. Therefore, standard accepted practice is that every patient with mild or uncomplicated biliary pancreatitis undergoes an elective cholecystectomy before discharge from hospital. Currently the operation can usually be performed by laparoscopy. In the mild interstitial edematous form of acute biliary pancreatitis, the laparoscopic cholecystectomy is usually performed between 4 and 7 days from onset of the illness and after the pain resolves, return of serum amylase or lipase to normal levels should not be the criteria used – rather good clinical impression. In contrast, in patients with severe necrotizing acute pancreatitis of biliary origin, cholecystectomy should be delayed for 3–6 months; recurrence is surprisingly rare and early intervention (within the first 2–3 weeks) increases the risk of superinfection of the necrosis.

Results of Surgery in Necrotizing Pancreatitis

Authors	Year	Number	Percentage of infected necroses	Mortality
Beger et al.	1988	95	39%	8%
Tsiotos et al.	1998	72	79%	25%
Branum et al.	1998	50	84%	54%
Fernandez del Castillo et al.	1998	64	56%	6%
Büchler et al.	2000	42	93%	21%

Potential Postoperative Complications

Hemorrhage
Sepsis
Abscess
Fistula (pancreas, small/large bowel, colon)
Ileus

Chronic Pancreatitis

Case 1

Male, 35, single, local government employee

History

The patient had been living with his widowed mother for years since his father's death from alcoholic cirrhosis. As a student, he had difficulties making friends, leading to steady alcohol consumption from the age of 16. At 25, he had his first episode of acute pancreatitis with admission to hospital. The patient was free from pain for 4 years. However, for the last 5 years, renewed and continual alcohol consumption began again with (at least) 4–5 bottles of beer and 2–3 cocktails daily. A second episode of pancreatitis occurred 2 years ago and since then at intervals of 4–6 weeks. His general practitioner had prescribed non-narcotic analgesics as required but there had been no major improvement. Two years ago, laparoscopic cholecystectomy was performed but without change in the pain syndrome. The patient's current referral was prompted by almost weekly attacks of pain which tended to occur after meals but usually in the late evening and sometimes during the night. The patient began taking opioid-type analgesics, i.e. codeine 60 mg q.i.d. or oxycodone 10 mg q.i.d. from his general practitioner on an intermittent basis.

Physical Examination

Patient in good general condition, slightly undernourished. Abdominal examination showed guarding and tenderness in the epigastrium but no peritonitis. Liver slightly enlarged, with lower edge 2 fingerbreadths below the costal arch.

Body weight 78 kg (170 lb), height 180 cm (6 ft).
Body temperature 37.2°C, heart rate 65/min, blood pressure 140/85 mm Hg.
Laboratory Parameters: Normal apart from an increased γ-GT to 60 U/l (normal ≤28 U/l). Amylase and lipase in the normal ranges, blood count unremarkable.

Ultrasonography Examination

Ultrasonography showed homogeneously hyperechoic patterns in liver consistent with fatty degeneration. Pancreas of normal size with isolated hyperechoic areas but without other significant changes. Abdominal vascular status and kidneys showed no abnormal findings.

ERCP

Moderate changes at the main pancreatic duct with irregular alterations in caliber. There were also changes in the first- and second-order side branches, consistent with a moderate chronic pancreatitis (according to Cambridge criteria: stage 2).

Contrast-Enhanced CT

Small cyst, 2 × 2 cm, in the head of the pancreas, no calcifications, pancreatic duct marginally dilated (4 mm).

Pancreatic Function Test

A serum pancreolauryl test revealed slight impairment in exocrine pancreatic function. Oral glucose tolerance in the normal range.

Diagnosis

Chronic pancreatitis with discrete functional and morphologic changes.

Management

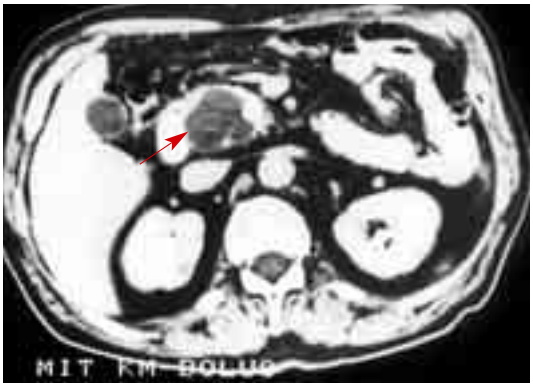
Strict abstinence from alcohol. Medication: oral pancreatic enzyme replacement at a dose of 20,000 lipase units per meal, non-steroidal anti-inflammatory analgesic drugs (rofecoxib 1 × 25 mg). Because the patient responded well to treatment, no further analgesic therapy. Put in touch with Alcoholics Anonymous. Patient instructed to attend the outpatient clinic for check-ups every 4 weeks.

Prognosis

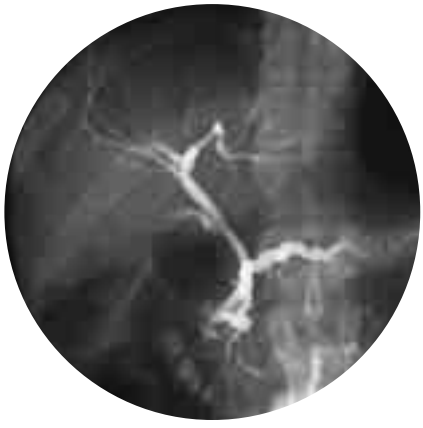
As the morphologic changes were slight, there is a good chance that the symptoms will take a favorable course and that there will be no further progression of the illness. His future behavior regarding alcohol will be the decisive factor in his prognosis.

Case Record

History	Intermittent epigastric, left upper abdominal pain, chronic alcohol consumption
Diagnosis	Early stage of chronic pancreatitis
Etiology	Alcohol
Laboratory parameters	Pancreatic enzymes normal, γ-GT 60 U/l, other laboratory parameters normal
Ultrasonography	Fatty liver, pancreatic parenchyma with irregular echo pattern
CT	Small cyst in head of pancreas without calcifications
ERCP	Chronic pancreatitis stage 2
Pancreatic function	Slight impairment of exocrine function, normal glucose tolerance
Treatment	Conservative, abstinence from alcohol, oral pancreatic enzyme replacement, analgesics
Course	Alleviation of pain
Prognosis	Good provided ongoing abstinence from alcohol



CT: Cyst (arrow) in head of pancreas near the duodenum, without calcifications.



ERCP: discrete dilatation of the pancreatic duct with irregular changes in caliber.

Case 2

Male, 45, divorced, 2 children, mechanic

History

Regular consumption of over 50 g alcohol daily for approximately 20 years. Eight years previously, marital problems ending in divorce. Thereafter extensive, uncontrolled alcohol abuse for 2 years. Subsequently, 7-year history of recurrent upper abdominal pain. Initially regular treatment with H_2 blockers and antacids for a suspected ulcer. One year ago, he had his first admission to hospital for acute pancreatitis. Since then, four episodes of acute pancreatitis, in each case self-limiting. Now another admission to hospital for acute pain in the upper abdomen, with increased serum amylase for the last 2 days.

Physical Examination

Thin patient, abdomen soft without peritonitis, deep palpation revealed tenderness in the abdomen with an area of guarding in the epigastrium. Marked scleral icterus.

Body weight 74 kg (164 lb), height 182 cm (6 ft 1 in).
Body temperature 37.2°C (rectal), heart rate 88/min, blood pressure 130/85 mm Hg.
Laboratory Parameters: Hemoglobin 12.4 g/dl, leukocytes 9.8 × 10^9/l, amylase 380 U/l, AST 45 U/l, ALT 38 U/l, GGT 131 U/l, alkaline phosphatase 891 U/l, bilirubin 2.1 mg/dl, creatinine 1.0 mg/dl, sodium 140 mEq/l, potassium 4.1 mEq/l, calcium 2.4 mmol/l, CRP 44 mg/l.

Ultrasonography

Gallbladder clearly enlarged. Dilatation of the extrahepatic bile ducts, diameter of common bile duct 9 mm. Entire pancreas enlarged with calcifications, especially in the head.

Diagnosis

Acute exacerbation of chronic pancreatitis, alcohol-induced.

Management

Admission to hospital for conservative treatment and for staging of the chronic pancreatitis.

ERCP

Extensive stenosis in the intrapancreatic portion of the common bile duct without evidence of malignancy, dilatation of the extrahepatic bile ducts. No cholelithiasis. Dilatation of the pancreatic duct and multiple calculi in Wirsung's duct and in the pancreatic parenchyma, especially in the head.

Contrast-Enhanced CT

Large inflammatory mass in head of pancreas in chronic pancreatitis with multiple cysts, dilatation of the pancreatic duct, multiple calcifications especially in the region of the head. Dilatation of the extrahepatic bile ducts.

Pancreatic Function Tests

The oral glucose tolerance test was normal with normal insulin secretion. In the pancreolauryl test, peak rise in the plasma fluorescein concentration to 2.5 µg/ml after 90 min (normal value over 4.5), hence diagnosis of exocrine pancreatic insufficiency.

Course

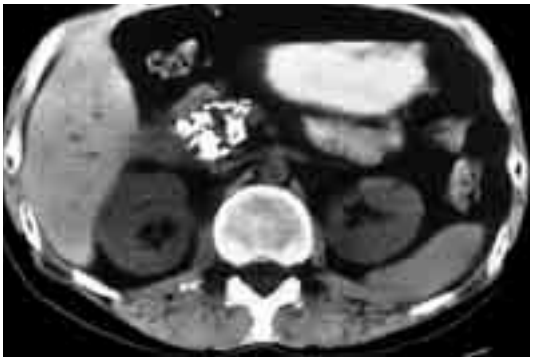
NPO, intravenous fluids and symptomatic management of an acute exacerbation of chronic pancreatitis resulted in rapid clinical improvement within 48 h. The confirmed extensive stenosis of the common bile duct and the inflammatory mass of the head of the pancreas were indications for surgery. On day 8 after admission, a duodenum-preserving resection of the head of the pancreas was performed, including an internal bile duct anastomosis and cholecystectomy. Uncomplicated postoperative course and discharge 17 days later.

Prognosis

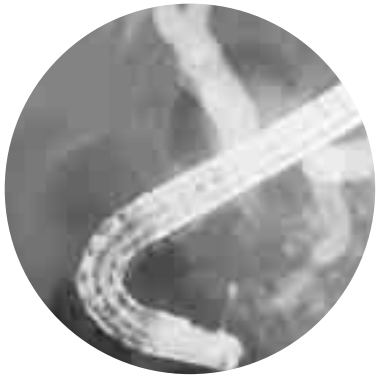
The prognosis is good provided there is abstinence from alcohol and reintegration into working life, 85% of patients will be permanently free from pain. The patient has been referred to the gastroenterology department for regular follow-up as well as to the substance abuse counselors.

Case Record

History	Recurrent upper abdominal pain, many years of alcohol abuse, ulcer treatment
Diagnosis	Chronic pancreatitis with inflammatory mass of head of pancreas and dilatation of the pancreatic and bile ducts
Etiology	Alcohol
Laboratory parameters	Amylase 380 U/l, γ-GT 131 U/l, AP 891 U/l, bilirubin 2.1 mg/dl, CRP 44 mg/l
Ultrasonography	Dilatation of the bile duct, calcifications
CT	Inflammatory mass in head of pancreas with extensive calcifications
ERCP	Stenosis of bile duct, massive dilatation of the pancreatic duct with stones (stage 3)
Pancreatic function	Moderate exocrine pancreas insufficiency with normal glucose tolerance
Treatment	After treatment of the acute exacerbation, duodenum-preserving resection of the head of the pancreas and internal bile duct anastomosis
Course	Discharge on 17th postoperative day
Prognosis	Good, provided abstinence from alcohol with 85% free of pain after 5 years



CT: inflammatory mass in head of pancreas with calcifications.



ERCP: stenosis and dilatation of bile and pancreatic ducts.

Case 3

Male, 55, married, one daughter, postal worker

History

The previous medical history included usual childhood diseases (mumps, varicella, scarlet fever). At 18 years of age, appendectomy, no other hospital admissions or serious illness. On closer questioning, the patient remembered occasional dyspepsia which bothered him during his training period and at the time of his daughter's birth. He had never consulted a doctor for this. His present disorder had begun 5 years previously. Initially, the patient felt exhausted, with a decline in performance, vomiting and polydipsia. The volume of his feces was very large, they were not formed, foamy, and floated. He was not alarmed until he lost a considerable amount of weight and consulted his physician. The diagnosis was diabetes mellitus with immediate insulin dependence. Shortly afterwards, he developed epigastric pain and was referred to a gastroenterologist. The patient drank alcohol only occasionally and was a nonsmoker.

Physical Examination

Patient had signs of acute and chronic weight loss. Skin and mucous membranes pale, abdomen soft, upper right abdomen tender, liver not enlarged. No peritoneal signs as clinically significant guarding.

Body weight 54 kg (130 lb), height 170 cm (5 ft 8 in).
Body temperature 37°C, heart rate 54/min, blood pressure 135/70 mm Hg.
Laboratory Parameters: Hemoglobin 10.5 mg/dl, MCV increased to 104 (normal < 94), leukocytes and platelets in the normal ranges. Fasting blood sugar 480 mg/dl, amylase 40 U/l, lipase 20 U/l.

Ultrasonography

Pancreas small, atrophic with many irregular echoes consistent with pancreatic calcifications.

CT

Small atrophic pancreas, multiple calcifications.

Pancreatic Function Test

The serum pancreolauryl test showed a maximum fluorescein concentration of 1.2 µg/ml indicating severe exocrine insufficiency.

Gastroduodenoscopy

Gastric ulcer (1.2 × 0.8 cm) at incisura. Histologic findings: benign ulcer, *Helicobacter pylori* positive.

Diagnosis

Chronic calcific pancreatitis (stage 3 with diabetes mellitus and steatorrhea), gastric ulcer with *H. pylori* infection.

Treatment

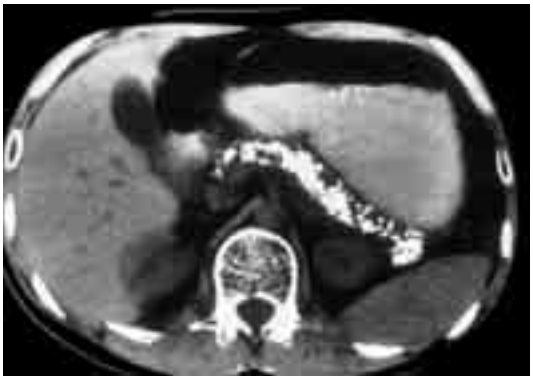
Treatment of the diabetes with insulin, 28 units in the morning and 14 in the evening, oral pancreatic enzyme replacement (dosage 20,000–40,000 lipase units/meal). Treatment of the ulcer: triple therapy for 1 week with omeprazole 2 × 40 mg, amoxycillin 2 × 1 g and metronidazole 2 × 500 mg. Omeprazole 20 mg for another 4 weeks until the ulcer had healed. For the macrocytic anemia, initially 1,000 µg cyanocabalamin intramuscularly with concomitant administration of fat-soluble vitamins as replacement for the fat-soluble vitamins not absorbed due to the diarrhea.

Prognosis

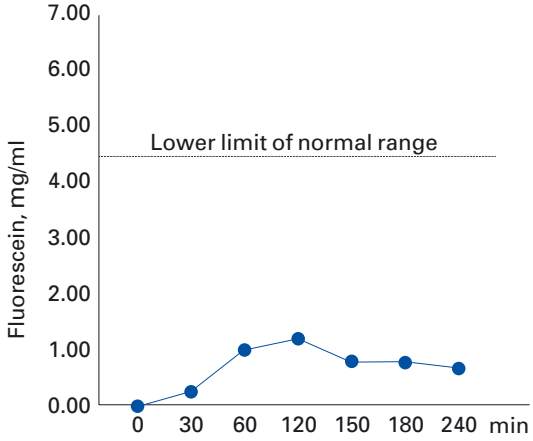
The exocrine pancreatic insufficiency and the insulin-dependent diabetes mellitus are irreversible; these factors will determine the future course of the disease. Good control of the pancreatic insufficiency and stabilization of diabetes are important end points.

Case Record

History	Currently no pain but steatorrhea and uncontrolled diabetes mellitus
Diagnosis	Chronic pancreatitis with end-stage exocrine and endocrine insufficiency; gastric ulcer
Laboratory parameters	Amylase 40 U/l, glucose 480 mg/dl
Ultrasonography	Pancreas small, multiple calcifications
CT	Small atrophic pancreas with multiple calcifications
ERCP	Not performed
Pancreatic function	Exocrine function severely impaired, insulin-dependent diabetes mellitus
Treatment	Insulin, oral pancreatic enzymes, diet, ulcer treatment
Prognosis	Guarded, dependent on control of diabetes and the exocrine pancreatic insufficiency



Chronic calcifying pancreatitis.



Pancreolauryl test. Highly pathologic reduction in the serum fluorescein levels.

An Atypical Case

Female, 53, married, housewife

History

A history of alcohol abuse for 8 years with recurrent abdominal pain for the last 5 years. In the past, four admissions to hospital for acute pancreatitis, the most recent 1 month earlier. Cholecystectomy 4 years previously. She had had recurrent bilateral pulmonary embolism and a duodenal ulcer 3 years ago. She has been abstinent from alcohol for the last 9 months with Antabuse therapy. Referral for pain refractory to treatment and suspected pancreatic neoplasm with an increase in the size of a mass in the head of the pancreas and extrahepatic cholestasis.

Physical Examination

Cachectic malnourished patient. Abdomen soft with tender mass in the epigastric region.

Body weight 43 kg (95 lb), height 160 cm (5 ft).
Body temperature 37.2°C, heart rate 76/min, blood pressure 105/70 mm Hg.
Laboratory Parameters: Hemoglobin 14.8 g/dl, leukocytes 11.0 $\times 10^9$/l, albumin 4 mg/dl, CRP < 2.5 mg/l, AST 123 U/l, ALT 191 U/l, γ-GT 88 U/l, alkaline phosphatase 148 U/l, amylase 182 U/l, CA 19-9 38 kU/l, INR 1.0.

CT

Compared with the previous CT 1 year before, enlargement of a mass in the head of the pancreas, currently 10 cm in diameter. Multiple calcifications in the head and body as well as several pseudocysts with maximum diameters of 1 cm. CT shows distinct dilatation of the intrahepatic and extrahepatic bile ducts.

ERCP

Wirsung's duct was dilated with marked irregularities of the walls and first- and second-order side branch dilatations. Dilatation of the pancreatic duct seen throughout the pancreas; biliary tree unable to be cannulated.

Pancreatic Function Test

Clearly pathologic reduction in pancreatic elastase in the feces. An oral glucose tolerance test revealed latent diabetes mellitus with 220 mg/dl after 2 h.

Diagnosis

Chronic calcifying pancreatitis with suspected neoplasm.

Treatment

Pylorus-preserving pancreatoduodenectomy with pancreatojejunostomy, hepaticojejunostomy, and duodenojejunostomy. Uncomplicated postoperative course. Discharged on the 16th postoperative day.

Pathologic Evaluation

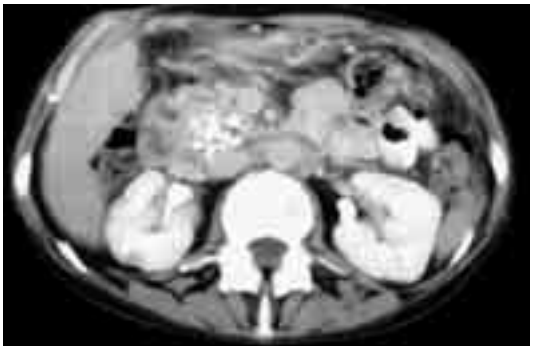
Histology: clearly chronic, markedly fibrosing atrophic chronic pancreatitis with periductal sclerosis and focal infiltration consisting mainly of lymphocytes and plasma cells. Special form of chronic pancreatitis that may be described as lymphoplasmocytic, sclerosing chronic pancreatitis. A variant of a primary sclerosing cholangitis (PSC) may be present. Autoimmune antibodies negative in suspected presence of a PSC variant.

Prognosis

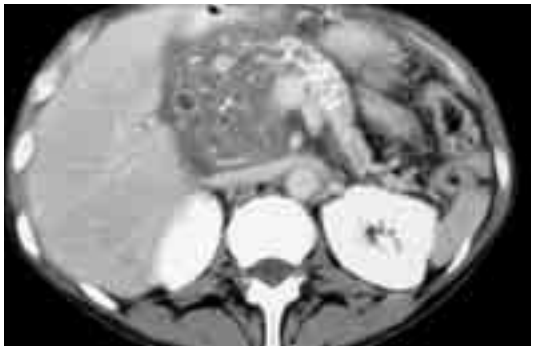
The patient continues to be essentially free from symptoms 4 years after the operation. Has regained 15 kg weight. To compensate for the exogenous pancreatic insufficiency, Creon, 1 capsule t.i.d. Acetaminophen as required, only occasionally.

Case Record

History	Treatment-resistant abdominal pain with known chronic pancreatitis for the last 4 years
Diagnosis	Chronic pancreatitis with enlarging mass in head of pancreas
Laboratory parameters	Hemoglobin 14.8 g/dl, leukocytes 11.0 $\times$ 10^9/l, albumin 4 mg/dl, CRP $<$2.5 mg/l, AST 123 U/l, ALT 191 U/l, γ-GT 88 U/l, alkaline phosphatase 148 U/l, amylase 182 U/l, CA 19-9 38 kU/l, INR 1.0, oral glucose tolerance test 220 mg/dl at 2 h consistent with latent diabetes mellitus
CT	Follow-up CT within 1 year showed increase in size of mass (10 cm) in head of pancreas; pancreatic calcifications and multiple pseudocysts; dilatation of pancreatic duct and entire biliary tree
ERCP	Stage 3 chronic pancreatitis with dilatation of the bile duct
Pancreatic function	Exocrine insufficiency, latent diabetes mellitus
Treatment	Pancreatoduodenectomy
Prognosis	Good



CT in comparison with one taken 1 year earlier. Clear increase in the chronically inflamed head of the pancreas with calcifications and multiple pseudocysts.



ERCP showing dilatation of the pancreatic and bile ducts.

Definition and Classification

Chronic pancreatitis differs from acute pancreatitis in that there are morphologic and functional changes, which, as a rule, progress to a chronic stage (pancreatic fibrosis, pancreatic insufficiency and diabetes mellitus). In isolated situations, the chronic changes persist without signs of progression or regression. It is often impossible to distinguish clinically between acute pancreatitis and the first manifestation of chronic pancreatitis although age may be a clue, as patients with acute pancreatitis tend to present at an earlier stage than those patients with established chronic pancreatitis. The current definition and classification of chronic pancreatitis are based on consensus conferences held in 1984 in Marseilles and Cambridge, both of which put emphasis on the characterization of the morphologic changes.

The clinical features of chronic pancreatitis are marked by recurrent episodes of acute epigastric pain; in a small number of patients, the episodes of pain do not occur as exacerbations but are chronic and persistent; only a small number of patients experience no pain, and the clinical presentation begins with steatorrhea and diabetes mellitus.

The morphologic characteristics of chronic pancreatitis consist of fibrosis, of varying degree and irregular distribution, resulting from destruction of the exocrine parenchyma. Depending on the stage of the disease, the morphologic lesions may be focal, segmental, or diffuse. The presence of calcifications is, as a rule, indicative of an advanced stage of chronic pancreatitis.

A special form of chronic pancreatitis – obstructive chronic pancreatitis – has as its morphologic feature uniform diffuse fibrosis of the parenchyma, but only distal to the obstruction with a normal proximal pancreatic gland.

Definition

Recurrent or persistent upper abdominal pain

Morphologic aspects:
Chronic inflammation of the exocrine pancreas with parenchymal fibrosis
Recovery never complete, generally a progressive functional impairment
Often complications in the course of the disease

Classification

Chronic pancreatitis with focal necrosis (fibrosis)
Chronic pancreatitis with segmental/diffuse fibrosis
Chronic pancreatitis with/without calcifications

Special form:
Obstructive chronic pancreatitis (e.g. neoplasm or postnecrotic, posttraumatic ductal stricture)

Etiologic Classification

Alcohol-related chronic pancreatitis

Non-alcohol-related chronic pancreatitis
- Hereditary
- Metabolic (hypercalcemia, hyperlipidemia)
- Autoimmune/infectious (Crohn's disease, viral infections, hepatitis B, Coxsackie)
- Idiopathic (juvenile/senile forms)
- Tropical
- Obstructive (pancreas divisum, postacute/posttraumatic ductal stenosis, choledochocele, periampullary duodenal diverticulum)
- Other causes

Pancreatic fibrosis (no association with chronic pancreatitis)
- Cystic fibrosis
- Insulin-dependent diabetes mellitus
- Hemochromatosis
- Advanced age (>70 years old)

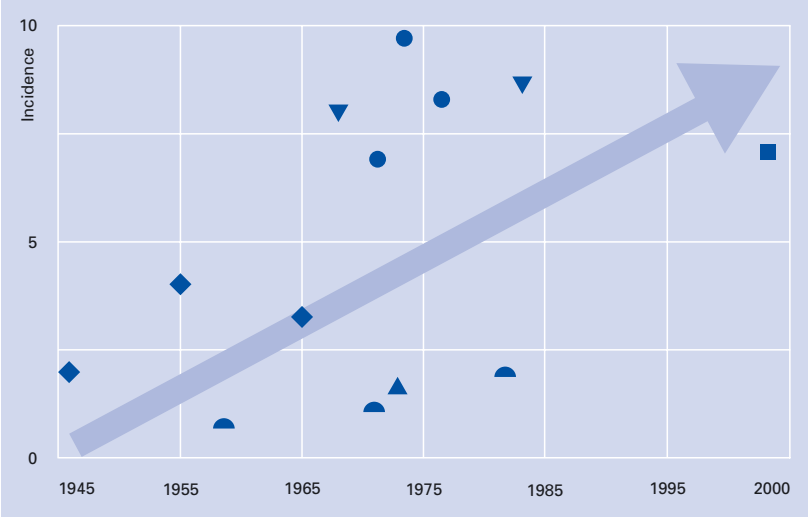
Epidemiology

A few studies have addressed the incidence of chronic pancreatitis. A prospective study from Denmark gives the incidence as 8.2 new diagnoses per 100,000 of the population and a prevalence of 27.4 cases per 100,000 population. If the prevalence of chronic pancreatitis is limited to a selected population with abdominal symptoms, the prevalence is 0.47%. Comparison with previous retrospective studies on incidence suggests a clear increase in incidence of the disease, which may reflect an increase due to increased alcohol consumption, but may be attributable to improved diagnostic procedures. Besides alcohol-induced chronic pancreatitis prevalent in Western countries, a tropical form of chronic pancreatitis occurs in African and Asian countries. This condition becomes clinically manifest as early as childhood and adolescence. No data are available on the incidence or prevalence of tropical pancreatitis.

Cancer Risk

The risk of developing a ductal adenocarcinoma is about 5% for patients with chronic pancreatitis. A follow-up study revealed a relationship to time with an incidence of developing carcinoma of about 2% in patients whose chronic pancreatitis had been diagnosed 10 years previously and of 4% in those whose illness was of 20 years' duration. Sex, country or cause of the chronic pancreatitis, on the other hand, appear to have no bear ing on the development of malignancy. A preoperative objective diagnosis of ductal cancer is rarely successful, and, as a rule, the malignant neoplasm is diagnosed or suspected intraoperatively and confirmed either by frozen section analysis or only later unsuspectingly on the permanent histologic sections of the resected specimen.

Incidence per 100,000 Inhabitants



Cancer Risk

Duration of chronic pancreatitis, years	Incidence of adenocarcinoma, %
10	1.8 (1.0–2.6)
20	4.0 (2.0–5.9)
Follow-up of 1,552 patients with chronic pancreatitis	

Etiology

The most frequent cause of chronic pancreatitis (75–90%) in Western industrialized countries is excessive alcohol consumption. Interestingly, only 10% of alcoholics develop chronic pancreatitis. Long-term alcohol consumption more often results in cirrhosis of the liver. This fact is probably associated with an as yet unknown genetic factor and generally, cirrhotics do not develop chronic pancreatitis and vice versa. Not every affected patient has clinically or socially evident chronic alcohol abuse. As the tolerance limits for alcohol differ substantially between individuals, 'relatively small' amounts of alcohol may be sufficient to induce pancreatic damage in some of those affected. The precise roles of other nutritional factors and their interaction with alcohol have not been accurately identified. Other metabolic factors that can induce chronic pancreatitis are hypercalcemia and chronic uremia, but usually to a much lesser degree. In addition, there is a now well-understood hereditary form of chronic pancreatitis, and there are also forms which still have not been identified etiologically and thus come under the term 'idiopathic chronic pancreatitis'.

A special form, chronic obstructive pancreatitis, occurs in rare situations in the presence of congenital anatomic variants, e.g. pancreas divisum, papillary stenosis, duodenal diverticuli, or after localized stricture of the pancreatic duct from neoplasms, trauma, or following necrotizing pancreatitis.

Molecular and genetic studies are becoming increasingly important in these disorders. Insight into the molecular mechanisms of the underlying disorders provides major diagnostic aids for etiologic classification, diagnosis, and planning of therapeutic options.

Etiology

Metabolic causes

Alcohol (75–90%)
Hypercalcemia (hyperparathyroidism)
Chronic uremia
Protein deficiency
Trace element deficiency
Dietary toxins
Smoking
Medicinal products (phenacetin)

Mechanical causes (special form of chronic obstructive pancreatitis)

Pancreas divisum
Annular pancreas
Papillary stenosis
Ductal scarring
Neoplasms
Duodenal diverticulum
Stricture of the pancreatic duct after severe acute pancreatitis or trauma

Familial hereditary causes

Autosomal dominant mutations

Cationic trypsinogen (codons 29, 122)

Autosomal-recessive mutations

SPINK1
Cationic trypsinogen (codons 16, 22, 23)
Cystic fibrosis transmembrane conductance regulator (CFTR)
α_1-AT

Idiopathic causes

Juvenile form
Senile form
Tropical form

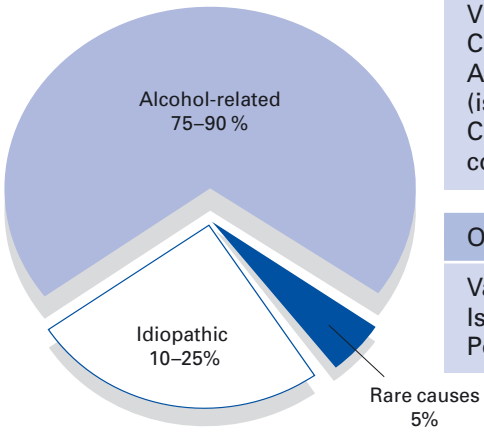
Immunological/autoimmune causes

Viral infections (hepatitis B, Coxsackie)
Autoimmune diseases (isolated, Sjögren's syndrome, Crohn's disease, ulcerative colitis, primary biliary cirrhosis)

Other rare causes

Vascular disease
Ischemia
Postradiation therapy

Incidence



Pathogenesis and Pathophysiology

Alcohol-Induced Chronic Pancreatitis

There appears to be a logarithmic relationship between the risk of developing chronic pancreatitis and the daily amount of alcohol consumed. The critical threshold of daily alcohol intake has been estimated to be about 40 g daily for women and 80 g daily for men, based on an exposure time of 5–15 years, with the decisive factor being the amount of alcohol and not the quality or type of the alcoholic beverage. Alcohol-induced chronic pancreatitis is first seen most often in young men aged only 20–30 years. A striking feature in the histories of these patients is that their alcohol consumption usually started about the time of puberty. This observation raises the question of whether the pancreas is especially sensitive to the toxic effects of alcohol during times of hormonal change. If excessive alcohol intake does not occur until adulthood, the latent period before the development of chronic pancreatitis appears to be about 10–20 years. Which other factors, apart from a potentially genetically predisposed sensitivity of the pancreas, enhance the toxic effects of alcohol are yet to be determined. Other cofactors under consideration include smoking, the presence of oxidative stress, a diet high in protein and fats, as well as a deficiency of trace elements such as zinc, copper and selenium.

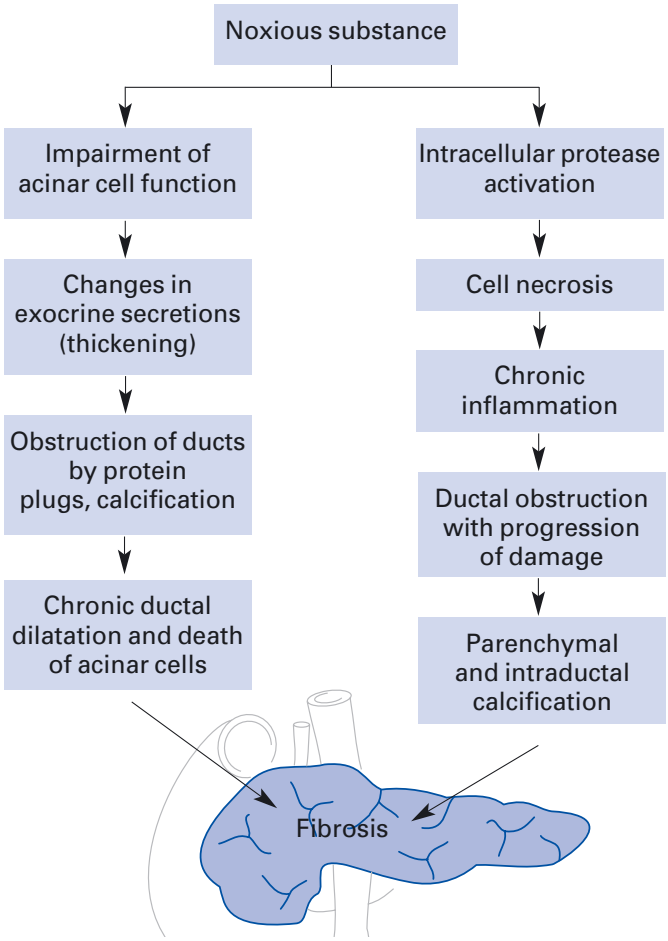
The pathologic mechanism that leads to development of chronic pancreatitis as a result of excess alcohol ingestion is not clear, and multiple hypotheses have been put forward. The most convincing of these is the hypothesis based on animal models, that chronic alcohol abuse results in a change in the composition of pancreatic exocrine secretions with secondary obstruction of the peripheral pancreatic ducts. In contrast, an alternative hypothesis based on pathologic changes in the human pancreas supports the concept that the alcohol-mediated autoactivation of proteolytic enzymes in the tissues results in cell death, fibrosis and scarring of the ducts.

Model of Primary Changes in Pancreatic Exocrine Secretion

Chronic alcohol consumption results in a decrease in pancreatic bicarbonate and water secretion and a concomitant increase in protein and calcium concentrations. These changes result in increased viscosity of the pancreatic exocrine secretions which cause protein plugs to form in the ducts arising from the pancreatic acini. As protection against calcification of these protein plugs, the pancreas secretes a pancreatic stone protein called lithostatin (molecular size 13,500 D). This glycoprotein has a central role in the prevention of the precipitation of calcium carbonate and thus in preventing the development of intraductal calcification. Genetically reduced synthesis of this protein results in an increase in the sensitivity of the pancreas to alcohol.

Intraductal calcifications are typical lesions of chronic pancreatitis and consist of a protein matrix enriched with lithostatin and surrounded by a shell formed of calcium carbonate. Obstruction of the ductal system induces dilatation and proliferation of the ductal epithelium, resulting in degeneration of the acini, local chronic inflammation, and eventual replacement of parenchyma with fibrosis.

Pathophysiology



Hypotheses on the Pathogenesis of Chronic Pancreatitis

Theories	Primary	Secondary
Obstruction Plug hypothesis	Changes in pancreatic secretions Lithostatin ↓	Ductal stones
Necrosis-fibrosis sequence	Recurrent exacerbations of acute pancreatitis with necrosis	Induction of fibrosis via growth factors (TGF_{α}, TGF_{β}), strictures
Toxic metabolic hypothesis	Direct damage of acinar cells	Fatty degeneration of acinar cells, cell necrosis, and fibrosis
Detoxification insufficiency	Increase in oxygen free radicals (oxidative stress) (impaired hepatic detoxification)	Impaired intracellular metabolism of the acinar cells → crinophagy, adverse effect on membranes → inflammatory response

Model of Primary Cell Necrosis (Necrosis-Fibrosis Sequence)

This hypothesis of a progressive necrosis-fibrosis sequence is based on the observation of progressive morphologic changes in different stages of chronic pancreatitis. This theory postulates that the pathogenesis involves recurrent intraparenchymal autoactivation of proteases with the resultant pancreatic necrosis giving rise to scarring (fibrosis), ductal strictures and intraductal and parenchymal precipitation of protein and calcium carbonate.

Alternative Hypotheses

Besides these two theories, some have postulated that fat accumulates within the acinar cells from chronic alcohol consumption, similar to that which occurs in the liver, which leads to the insidious transition to fibrosis.

Yet another hypothesis attributes the disease to impaired hepatic detoxification. This concept incriminates a state of oxidative stress with increased production of oxygen free radicals and reactive toxic intermediary products, resulting in inhibition of intracellular metabolism within the acinar cell. Oxidative stress leads to fusion of liposomes and zymogens (crinophagy) and peroxidation of membrane lipids. These events stimulate a local inflammatory reaction which leads to chronic pancreatitis.

Current knowledge suggests that alcohol-induced toxicity for the pancreas is multifactorial in nature, because there are such diverse possible interindividual differences with regard to the stage and the progression of disease despite similar intakes of alcohol.

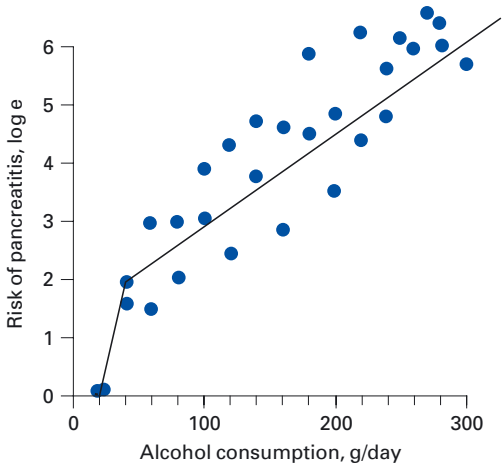
Tropical Chronic Pancreatitis

It appears that different factors are involved in the pathogenesis of tropical chronic pancreatitis found chiefly in India. First, the disease occurs in association with a deficiency of dietary protein. A deficiency of dietary protein alone is not sufficient but rather it is the latter's combined interactions with other dietary substances, trace elements and toxins. It has not been confirmed whether or not cyanide-containing cassava, consumed chiefly in India, is of primary importance. Through the inhibition of enzymes such as superoxide dismutase and catalases, it has been postulated that cassava may lead to a state of oxidative stress via an increase in oxygen free radicals with subsequent damage to acinar cells.

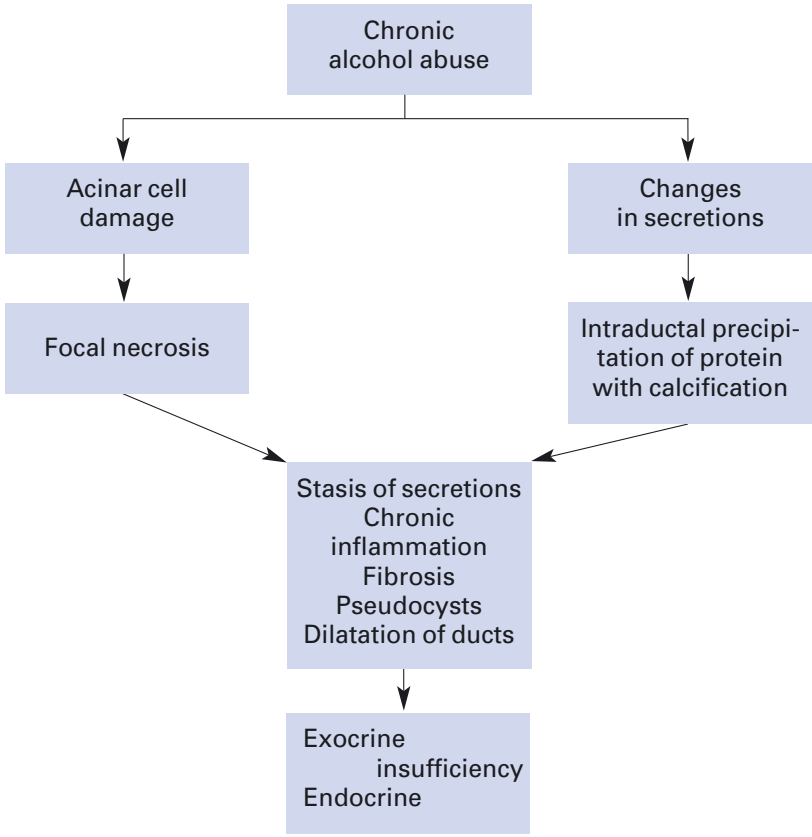
Metabolic Causes of Chronic Pancreatitis

One postulated metabolic cause of chronic pancreatitis is the hypercalcemia syndrome associated with primary hyperparathyroidism. Increased serum calcium concentration is believed to induce direct damage to acinar cells and increased secretion of calcium results in intraductal stone formation. Almost 70% of patients with chronic uremia, especially those who are dependent on dialysis, develop varying degrees of fibrosis of the pancreas with formation of calcifications. The mechanism of increased pancreatic fibrosis in these patients with dialysis-dependent chronic renal failure has not been fully elucidated. Some of these patients have recurrent bouts of abdominal pain, but pancreatic insufficiency is rarely seen.

Risk of Pancreatitis in Relation to Alcohol Consumption



Alcohol-Induced Chronic Pancreatitis



According to our current knowledge, hyperlipidemia may be excluded as a cause of chronic pancreatitis.

Idiopathic Chronic Pancreatitis

The primary characteristic of idiopathic chronic pancreatitis is that chronic alcohol consumption is excluded as a cause. Idiopathic chronic pancreatitis occurs in two forms, a juvenile and a senile form. The pathophysiology of pancreatic injury in either form is not known.

Familial Chronic Pancreatitis

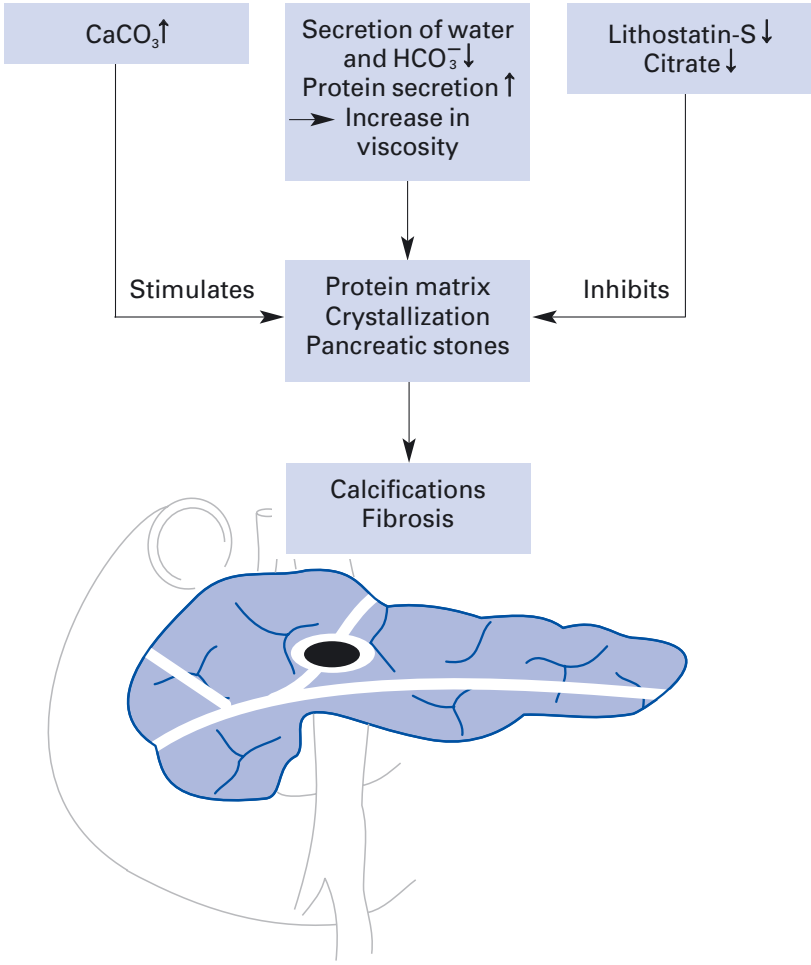
This rare form of chronic pancreatitis usually manifests itself between the ages of 5 and 15 years. A genetic predisposition to development of this form of chronic pancreatitis was first described in 1952, and, in 1996, a mutation was found in the cationic trypsinogen gene which appears to trigger familial chronic pancreatitis. The discovery of this genetic mutation has opened a fascinating, new field of the genetics of chronic pancreatitis. Further additional mutations have been discovered, such as mutations of CFTR and serine protease inhibitors, e.g. Kazal type 1 (SPINK1).

Cationic trypsinogen has a central role in the digestion of dietary proteins as well as in the activation of other digestive enzymes. Consequently, premature intracellular activation of trypsinogen within the pancreatic acinar cell leads to activation of the other enzymes, which may ultimately result in autodigestion. When the human cationic trypsinogen gene, located on chromosome 7, is appropriately mutated, the autosomal dominant form of the disease occurs. The most frequent mutations have been described in codons 29 (exon 2) and 122 (exon 3) of the cationic trypsinogen gene. The codon 122 mutation leads to an R122H mutation (replacement of an arginine by histidine for amino acid 122 of the protein). Activated trypsin can no longer hydrolyse itself intracellularly and is thus not inactivated. Other mutations have been described for codons 16, 22, 23 and 29. An autosomal recessive mutation is the SPINK1 (PSTI) mutation. PSTI (serine protease inhibitor) Kazal type 1 is a 56-amino acid peptide which specifically inhibits prematurely activated intracellular trypsin. Inactive trypsinogen and SPINK1 are both synthesised in the acinar cells of the pancreas in a ratio of 5:1. Premature trypsinogen activation occurs regularly within the acinar cells and risks activating other intracellular pancreatic enzymes as the initial stage of autodigestion during onset of acute pancreatitis. SPINK1/PSTI normally inhibits up to 20% of prematurely activated trypsin and also its mutants. When SPINK1 is mutated, inhibition of intracellular active trypsin is ineffective; the resultant free trypsin may be activated to trigger the inflammatory cascade and thus, via recurrent exacerbations of acute pancreatitis, gives rise to chronic pancreatitis.

Obstructive Chronic Pancreatitis

This form of chronic pancreatitis is caused by congenital and acquired strictures of the pancreatic duct, congenital anomalies (pancreas divisum, annular pancreas), neoplasms, inflammatory and cicatricial stenosis of the papilla of Vater, and the effects of trauma of the pancreas causing ductal injuries leading to ductal stenosis. The characteristic manifestation of stenosis-induced pancreatic damage is a uniform postobstructive

Factors Involved in Stone Formation in the Pancreas



Data from the Identification of Mutations in Pancreatitis-Associated Genes

Etiology of pancreatitis and clarification of the risks of developing the disease; possibility of a rational classification; early diagnosis of diseases of the pancreas; clarification of the progression and prognosis of diseases of the pancreas; information on genetic interactions; development of new therapeutic concepts; genetic counseling

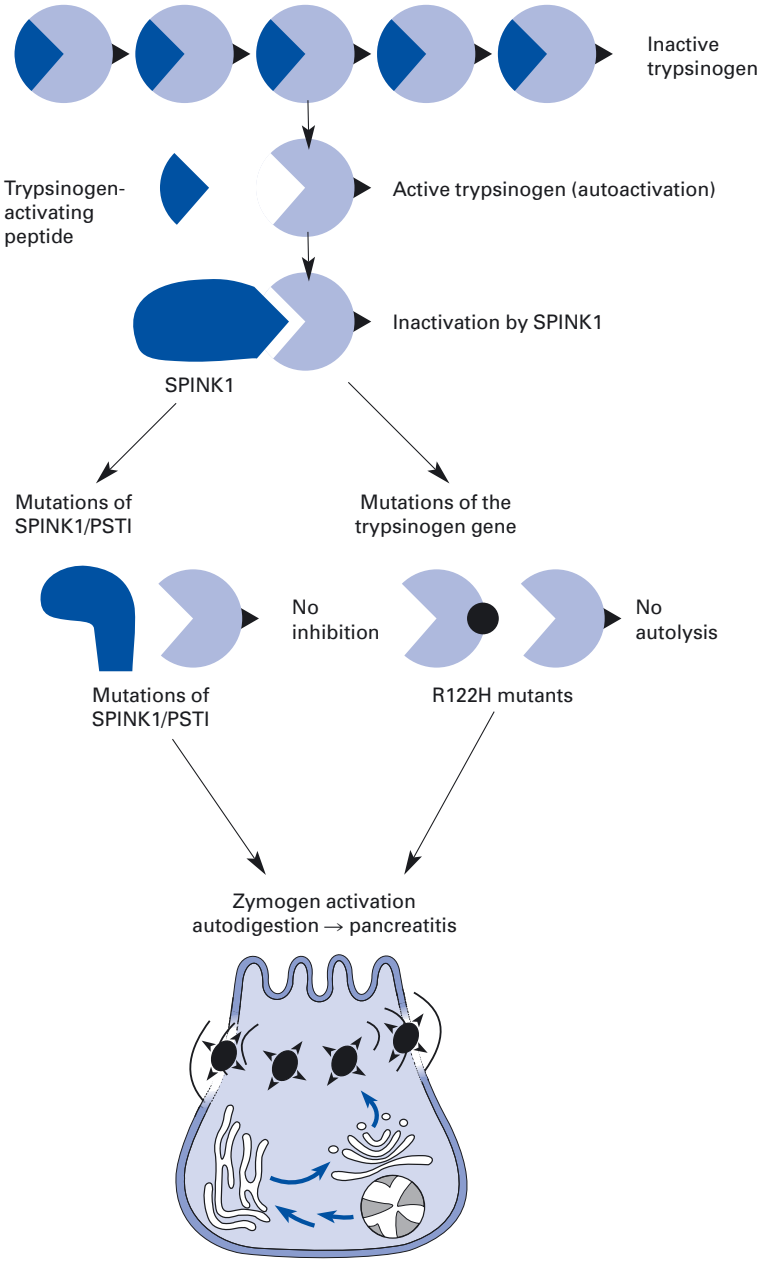
diffuse fibrosis only rarely associated with formation of intraductal protein plaques. The condition does not progress to the calcifying form. Development of chronic obstructive pancreatitis is initially marked by a stasis of the secretions distal to the stenotic ductal lesion(s) and the formation of edema in the gland. As is apparent from clinical case studies, pain usually occurs only at the beginning of this disease process and is thus transient in this form of chronic pancreatitis. Pancreatic dysfunction is primarily manifest as insufficiency of exocrine function and at a later date also by endocrine function. Chronic obstructive pancreatitis secondary to gallstone disease is rare. The presumed pathogenesis may involve either scarring of the pancreatic duct due to acute biliary pancreatitis or damage to the papillary sphincter mechanism (e.g. during the passage of a gallstone with injury to the papilla) with resultant ampullary stenosis. The most frequent of the congenital pancreatic anomalies is pancreas divisum. This condition may, in rare instances, impair drainage of exocrine secretions because of too narrow a minor duodenal papilla, resulting in obstructive changes in the dorsal segment (dorsal duct syndrome).

Duodenal diverticula in a juxtapapillary or 'peri Vaterian' location cause obstruction of pancreatic exocrine drainage due to intermittent filling of the diverticulum with chyme or detritus. Duodenal diverticula may be associated clinically with recurrent acute attacks of pain. Annular pancreas is a congenital anomaly that causes duodenal obstruction, usually in childhood, more rarely in adults. Chronic obstructive pancreatitis may develop in the annular segment in adults, but this is quite unusual.

Interstitial Chronic Pancreatitis

This form of chronic pancreatitis occurs very rarely after certain viral infections (hepatitis, Coxsackie) or in the setting of an underlying systemic disease (e.g. Crohn's disease) and presents clinically as severe persistent pain. Morphologically, the condition is marked by massive lymphocytic infiltration of the pancreatic parenchyma.

Intracellular Trypsin Activation and Genetically Induced Abnormalities of the Intracellular Protective Mechanisms

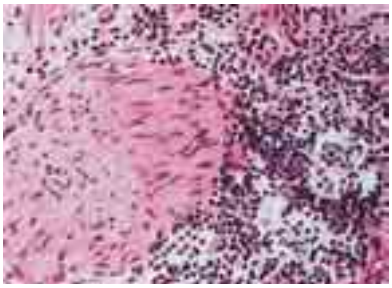


Pathogenesis of Pancreatic Pain

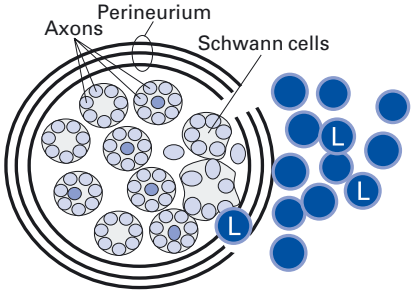
Pain represents the cardinal symptom of chronic pancreatitis. Numerous studies carried out with the objective of determining the progression of the development of pain in this condition have led to many different theories. The pain has been attributed to increased intraductal pressure, increased pancreatic intraparenchymal pressure (a form of 'compartment syndrome'), parenchymal or intraductal calcifications, and acute exacerbations of the underlying illnesses. However, none of these concepts have provided a definitive answer.

Recently, studies using light and electron microscopy have confirmed specific neural changes in chronic pancreatitis which could represent the morphologic correlate of the pain syndrome. Characteristically, nerve fibers in chronically inflamed tissues are increased in numbers and thickness and exhibit ultrastructural changes at the perineurium, which constitutes the barrier between the nerve and adjacent inflamed tissue. Lymphocytic infiltration is a regular occurrence with associated disruption of the integrity of the perineurium, consistent with a local pancreatitis-associated neuritis. In addition, increases in sensory neurotransmitters (substance P and CGRP) have been found. These newly recognized phenomena open a new insight as to the cause of pain in chronic pancreatitis, originating in the intrapancreatic nerves. Therapies may thus be directed at this concept of inflamed intraparenchymal nerves in the pancreas. Relatively recent studies using techniques of molecular biology have validated this pain neogenesis concept. Growth-associated protein 43, for instance, a neural growth factor, has been found to be overexpressed in chronically inflamed pancreatic tissues in comparison with normal control tissue.

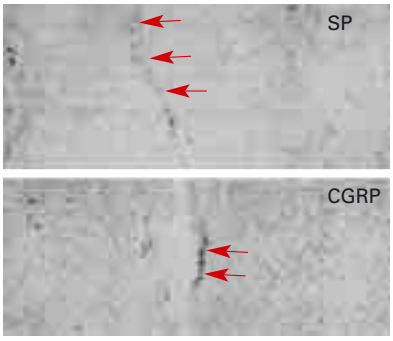
Pathogenesis of Pain



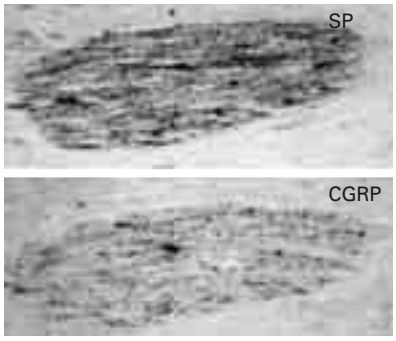
Pancreatitis-associated neuritis.



L = Lymphocytes.

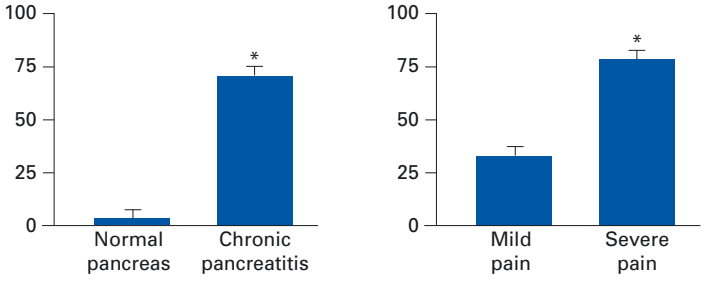


Normal sensory nerves in the pancreas.



Histologic picture. Same magnification as left. Grossly enlarged nerves in chronic pancreatitis with increased expression of SP and CGRP.

Growth-Associated Protein 43



Relationship between GAP-43 and severity of pain.
*= Significant difference.

Pathology

Any description of the morphologic changes of chronic pancreatitis must take into account the gross morphology as well as the degree and type of histologic changes. The changes may be isolated, segmental or diffuse. The lesion may manifest as areas of fibrosis, inflammatory infiltrates, calcifications or pseudocysts.

The classic histologic picture of chronic pancreatitis is one of progressive changes in the acinar and ductal tissues. In the early stages of the disease, the tissue damage is focal in character with involvement of the lobules and protein precipitation in the small pancreatic ducts. The ductal epithelium shows either hypertrophy, hyperplasia, metaplasia, or atrophy with associated periductal fibrosis. In addition, histologic examinations show inflammatory infiltrates with predominantly neutrophils in the tissue.

The endocrine compartment of the pancreas (the islets of Langerhans) is also eventually involved in the progressive fibrotic process involving the exocrine parenchyma. Light microscopy shows that the islets remain well preserved for a long time in areas traversed by scars, whereas using immunohistochemistry, there are decreases in the insulin-producing β cells and changes in the glucagon-forming A cells and the pancreatic polypeptide (PP) cells, even in less advanced stages. The degree of histomorphologic damage does not always correlate with the extent of the residual endocrine function.

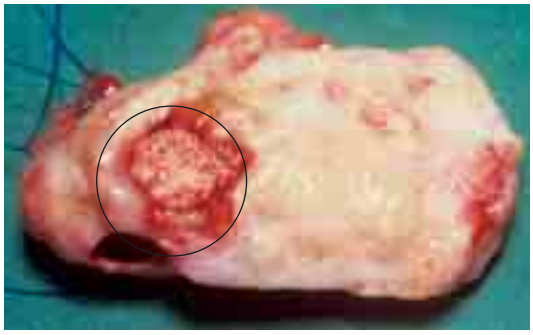
In the stages of inflammatory recrudescence associated with a chronic inflammatory process, the pancreas frequently shows a macroscopically evident enlargement and should be distinguished from neoplasm, especially in the head of the pancreas. In a subgroup of patients with chronic pancreatitis, the inflammatory process takes place largely in the head of the pancreas, with involvement (compression) of adjacent organ structures. The chronically inflamed head of the pancreas acts as the 'pacemaker of the disease'. Later in the course of the disease, the gland is, if anything, reduced in size, with extensive loss of endocrine and/or exocrine function.

Segmental scarring of the head of the pancreas with relatively localized involvement of the anatomic groove or sulcus between the head of the pancreas, the duodenum and the common bile duct is known as segmental pancreatitis or 'groove' pancreatitis; on occasion, differentiation from pancreatic carcinoma may be difficult.

Pathology

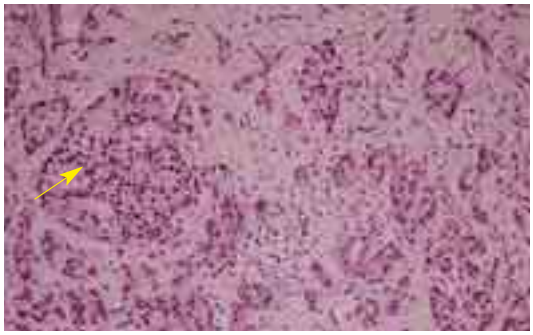
Site	Lesions
Isolated Segmental Diffuse	Fibrosis Infiltrates Calcifications Pseudocysts Atrophy

Macroscopic Picture



◯ = Stone in the pancreatic duct with almost total fibrosis (preparation after duodenum-preserving resection of the head of the pancreas).

Histology



Chronic fibrosing pancreatitis with intact islets of Langerhans (arrow).

Clinical Aspects

The main clinical symptoms of chronic pancreatitis include abdominal pain, maldigestion with steatorrhea, and in the later stages of the disease diabetes mellitus. These symptoms do not coexist until the late stage of the disease. By the time pancreatic insufficiency manifests, it is not unusual for the pain to become less severe or to have even disappeared altogether ('burned out').

Pain

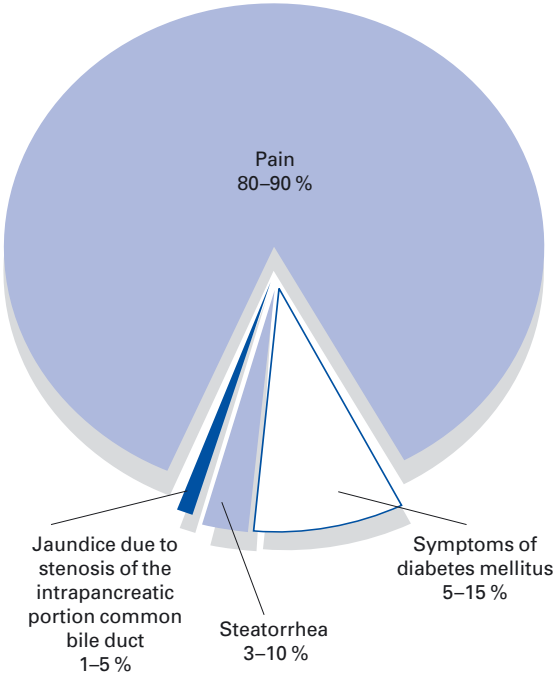
In the initial stage and over the course of many years, chronic pancreatitis is usually marked by distressing episodes of pain. The pain usually occurs in the epigastric region and upper abdomen and is described by a third of the patients as radiating straight through to the back. The most characteristic feature of the pain initially is its episodic occurrence; the first episodes are often indistinguishable from those of acute pancreatitis and as a rule precipitate admission to hospital. In most patients, the initial pain attacks are separated by long intervals (one or two episodes per year). From the second or third year onwards, however, the episodes of pain at this stage of the disease become more frequent and may progress to a chronic intermittent form of pain, the patients typically report 1–2 pain episodes per week, which often last for hours and have no direct association with any triggering event. In contrast to other causes of epigastric pain, only a small group of patients with chronic pancreatitis complain of pain associated with food intake. As a rule, the pain usually manifests itself many hours after the last ingestion of food. The treating physician should obtain accurate data on the patient's individual pain syndrome so as to target therapeutic measures accordingly. In about one third of patients, the pain is chronic in nature from the start, with frequently recurring attacks, often several in 1 week and sometimes even daily. This group of patients unfortunately develops early dependence on analgesics and often the use of opiates.

The pain is described as a lancinating boring pain, usually not dull-like, and on occasion even cramp-like. The characteristics of the pain are not pathognomonic and ultimately may prove to be a real challenge to the clinician to rule out other organic or functional disorders of the upper gastrointestinal tract in non-alcoholics with no predisposing factors for chronic pancreatitis. Not infrequently, patients have been treated for years with presumed lumbar-spinal syndromes because of the pain being felt predominantly in the back, before their condition is diagnosed appropriately as 'chronic pancreatitis'.

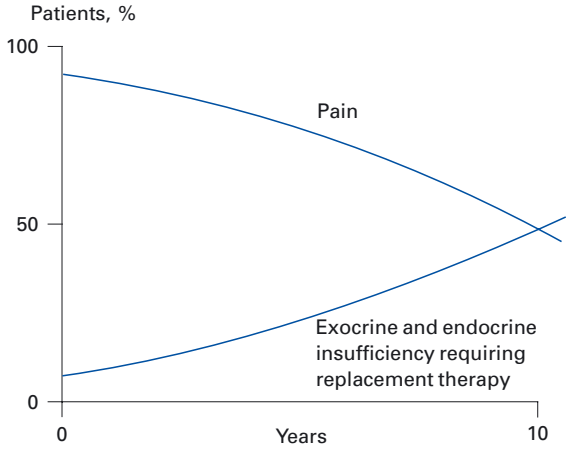
Exocrine Pancreatic Insufficiency

The clinical signs of pancreatic insufficiency which consist of fatty, floating, nonformed frothy stools (steatorrhea) do not occur until the condition is in a far advanced stage, i.e., when at least 90% of the pancreas has been destroyed by the chronic inflammatory process. Even at this stage, fatty stools may not be present if the patients, as a result of pain or a change in their diet, do not consume sufficient fat ($\geq$80 g fat daily) in their diet to lead to steatorrhea. In patients with chronic obstructive pancreatitis, especially if the disease involves ductal obstruction near the papilla, markedly impaired digestion secondary to virtual absence of exocrine secretions entering the duodenum may lead to a rapid onset of weight loss.

Cardinal Signs/Symptoms



Burnout Theory (Freedom from Pain)

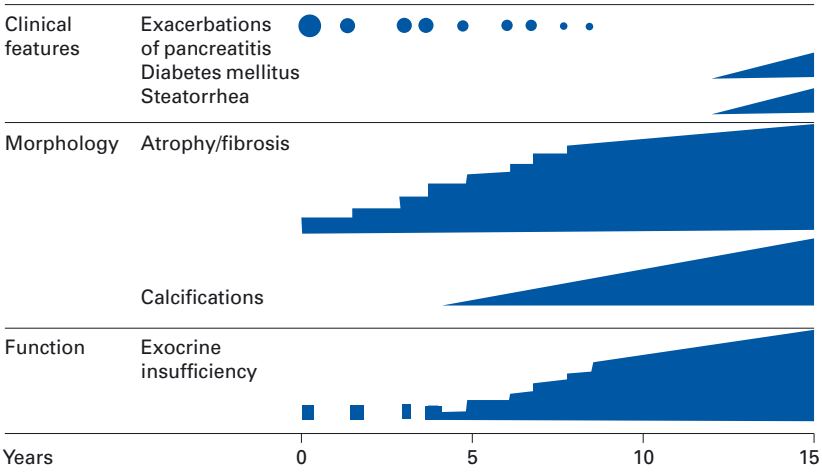


Diabetes mellitus

Diabetes mellitus develops later in the natural history of the disease than exocrine insufficiency. There are some exceptions to this general rule: for instance, in idiopathic pancreatitis that occurs in the elderly (senile chronic pancreatitis), the appearance of exocrine pancreatic insufficiency and diabetes mellitus may show a close temporal relationship.

Weight loss, a frequent finding in the advanced stages of chronic pancreatitis when exocrine and endocrine insufficiency are present, is a rare occurrence in the earlier stages of chronic pancreatitis when the pain is the dominant feature. In this stage of the disease, weight loss is most likely to occur in those patients who maintain a high alcohol consumption and have symptoms, such as nausea and vomiting. Pain associated temporally with food intake tends to be rare, and thus weight loss is unusual. When weight loss is marked, one should suspect another cause, such as an underlying pancreatic cancer. The spectrum of presentation in chronic pancreatitis includes a number of complications discussed in the next section.

Natural Course



Progression of fibrosis up to the end stage; occasionally patients have no progression of the chronic inflammation.

Complications

- Pseudocysts with or without compression of adjacent organs
- Obstruction of the intrapancreatic common bile duct (jaundice)
- Obstruction of the pancreatic duct
- Splenic vein thrombosis
- Pleural effusion
- Ascites
- Hemorrhage (e.g. pseudoaneurysm)
- Portal vein thrombosis (portal hypertension)
- Sinistral portal hypertension

Rare:
- Duodenal stenosis
- Colonic stenosis

Signs and Symptoms of Complications

Nausea, vomiting	Duodenal stenosis
Jaundice	Compression of intrapancreatic portion of common bile duct
Gastrointestinal bleeding	Gastric varices Esophageal varices Hemosuccus pancreaticus

Complications

Pancreatic pseudocysts, stenosis of the common bile duct, and stenosis of adjacent structures (duodenum, portal or splenic vein, colon) also occur in chronic pancreatitis. If pseudocysts of 2 cm in size are included, these are found on ultrasonography or CT in almost half of all patients with chronic pancreatitis. Unlike the acute peripancreatic fluid collections found in patients with acute pancreatitis that often resolve, pseudocysts occurring in the setting of chronic pancreatitis rarely regress. On the other hand, these cysts initially do not represent a danger to the patient unless they reach sizes >6 cm that may lead to complications, such as compression of the duodenum or the bile duct. Chronic pancreatitis of many years' standing as well as the familial form involve a substantially higher risk of the development of pancreatic carcinoma. The incidence of adenocarcinoma in patients with chronic pancreatitis over a 10-year period of follow-up is approximately 5%.

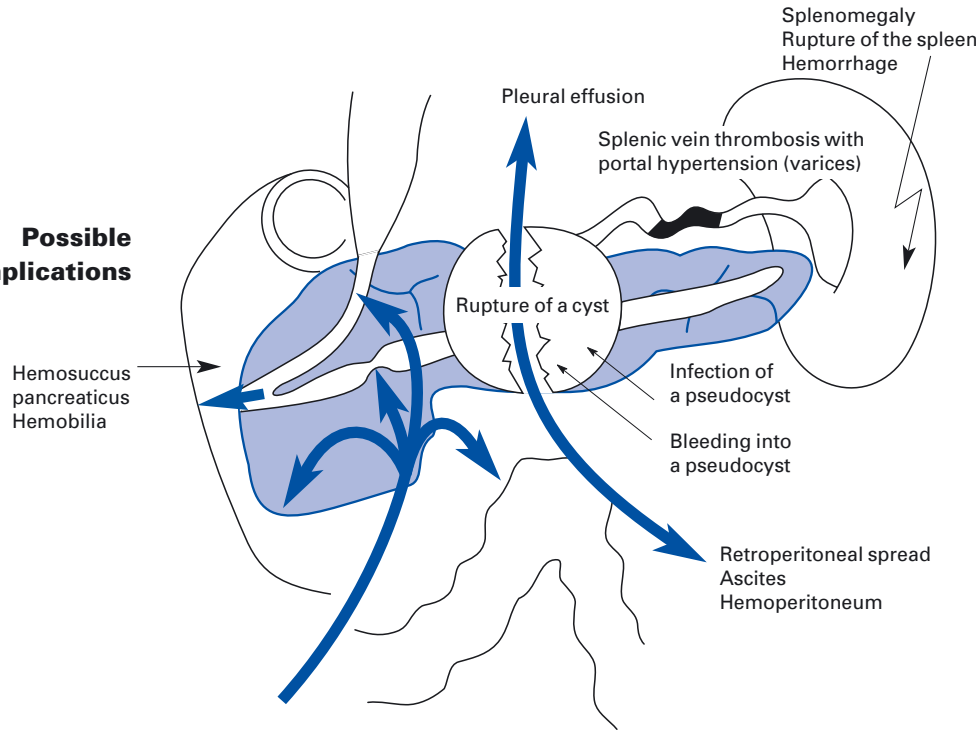
Stenosis of the common bile duct is an important finding, the incidence of which varies from 10 to 40% depending on the definition used. The extent of stenosis differs widely; it is caused by fibrotic stenosing reaction of the pancreatic tissue surrounding the intrapancreatic portion of the common bile duct, by external compression due to an inflammatory tumor in the head of the pancreas, or by a pseudocyst. This stenosis may be evident only by a rise in alkaline phosphatase or bilirubin, but occasionally it appears as clinical jaundice. Stenosis of the intestinal tract occurs predominantly in the duodenal region; stenosis of the colon occurs in extremely rare cases. Extrahepatic splanchnic venous stenosis or thrombosis may also occur and lead to problems with gastrointestinal bleeding discussed below.

In very rare instances, pleural effusion or ascites may develop in association with chronic pancreatitis, usually related to a pancreatic ductal disruption. The diagnosis of a pancreatic cause of such effusions may be confirmed by determining the presence of pancreatic enzymes in these secretions.

Peptic ulcers, especially duodenal ulcers, are more common in patients with chronic pancreatitis. This observation is probably due to the fact that the impaired secretion of pancreas-derived bicarbonate into the duodenum may not adequately buffer the acid emptied into the duodenum from the stomach. *Helicobacter pylori* infection, a major factor in the pathogenesis of peptic ulcers, occurs with the same frequency in patients with chronic pancreatitis as in the general population.

Gastrointestinal bleeding as a result of chronic pancreatitis may be a consequence of the increased consumption of analgesics (nonsteroidal anti-inflammatory drugs) with related gastrointestinal side effects (ulcer/erosion). Segmental or sinistral portal hypertension resulting from splenic vein thrombosis may be complicated by bleeding into the stomach from gastric varices, and very rarely from duodenal varices. Bleeding from the pancreatic duct into the duodenum, although rare, may result from erosion of a blood vessel or a pseudoaneurysm within a pseudocyst. This type of bleeding is termed hemosuccus pancreaticus.

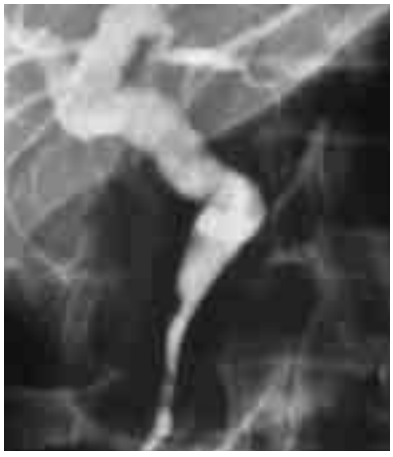
Possible Complications



Stenosis
Common bile duct → Obstructive jaundice, cholangitis
Pancreatic duct → obstructive pancreatitis
Duodenum → vomiting
Colon → colonic obstruction (partial)
Portal system → portal hypertension
As a result of pseudocyst or compression/spread of chronic inflammation

Duodenal or Common Bile Duct Stenosis

Passage of contrast medium with duodenal stenosis in a patient with a chronic inflammatory tumor of the head of the pancreas.



ERC showing common bile duct compression complicating a chronic inflammatory tumor of the head of the pancreas.

Diagnosis

During the physical examination, palpation may elicit pain in the epigastrium or periumbilical region. Splenomegaly in the context of splenic vein thrombosis is also rare. With severe common bile duct stenosis, jaundice may be evident. Most often, however, the clinical examination reveals no clinical findings and the diagnosis of chronic pancreatitis requires clinical acumen based on the entire clinical presentation. For this reason, the clinician has to rely on the use and correct interpretation of special investigative procedures including sensitive imaging techniques available as diagnostic aids, often complemented by pancreatic function tests.

Imaging Procedures

Progression of the inflammatory process, which is initially focal, becomes more segmental in the course of the disease and eventually becomes diffuse in the end stage. An exception is chronic obstructive pancreatitis in which the focal obstruction of the pancreatic duct leads to chronic pancreatitis *only* distal to the site of the stricture. It is impossible in the early stages of chronic pancreatitis, when the focal lesions represent the sole morphologic finding, to confirm the diagnosis with any of the methods currently available. The treating physician is thus obliged to repeat the imaging procedure over the course of 4–6 months when indicated by pancreatic type pain and the history of alcohol consumption.

A plain film of the abdomen in the advanced stages of chronic pancreatitis can show calcifications in the pancreas. Noninvasive methods, those that cause little or no discomfort to the patient, should be used initially for the diagnosis, e.g. ultrasonography, CT, or MRI.

Ultrasonography

This method, either transabdominal or endoscopic, often provides good visualization of the pancreatic parenchyma and also reveals changes in the pancreatic ductal system. In addition, it may visualize complications related to involvement of peripancreatic structures such as common bile duct dilatation, splenomegaly, or pseudocysts. As regards sensitivity, ultrasonography and CT are inferior to ERCP. The detection of chronic pancreatitis requires segmental changes in the normal parenchymal architecture leading to an echo pattern that appears irregular or to a segmentally or globally enlarged gland. These criteria are, however, limited regarding specificity. Increased or irregular fat inclusions, for example, or fibrotic changes in the elderly, may lead to a false-positive diagnosis of chronic pancreatitis. Pathognomonic signs are pseudocysts, irregular ductal dilatation, and calcifications. During this examination, it is possible to perform Duplex ultrasonography, which allows the non-invasive visualization of direction and flow of blood within blood vessels (e.g. portal vein problems).

Endoscopic Ultrasonography

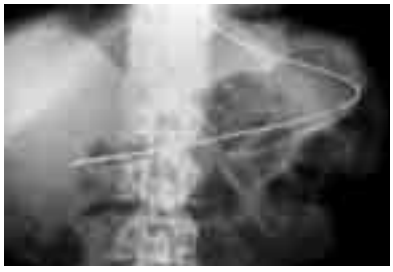
Endoscopic ultrasonography (EUS) has been introduced in gastroenterology departments as a new diagnostic method in recent years. Its value

Diagnosis

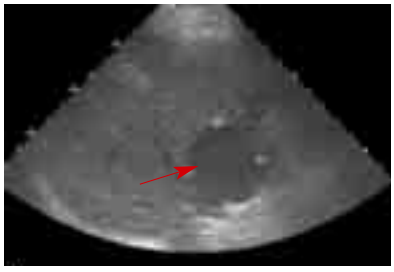
Morphology	Pancreatic function
Specific view of the pancreas Ultrasonography CT Endoscopic ultrasonography ERCP MRI	Quantitative determination of fecal fat content Enzyme assay in the feces (e.g. elastase-1) Indirect pancreatic function test (e.g. PLT) Direct pancreatic function tests Oral glucose tolerance test

Ultrasonography

Irregular organ contours
Marked changes in organ size (swelling, atrophy)
Irregular echo pattern
Cysts
Ductal dilatation
Calcifications



Specific view of the pancreas showing calcifications in the pancreas.



Visualization of a pancreatic pseudocyst (arrow) on ultrasonography.

Erythema included by intense heat application.

in the diagnosis of chronic pancreatitis is still being validated. EUS allows demonstration of cysts, stenosis, and dilatation of the pancreatic and common bile ducts, and also calcifications and stones in the pancreatic duct. Like other imaging procedures, EUS has difficulty distinguishing between malignant and benign pancreatic tumors, but may aid in staging of disease.

CT

CT shows many of the same changes as those seen by ultrasonography. Here, too, the emphasis is on visualization of the parenchyma, but the assessment concentrates on the organ density (Hounsfield units) rather than the echo pattern. The advantage of CT lies in the better visualization of the pancreas in distinction from the surrounding organs, especially in patients who are obese or in whom the pancreas cannot be visualized well due to overlying intestinal gas, where transabdominal ultrasonography reaches the limits of its technical possibilities. Spiral CT, together with intravenous contrast media, will complement conventional CT allowing it to compete with MRI.

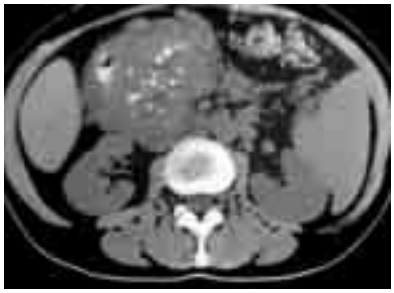
MRI

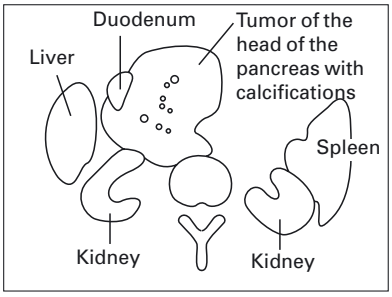
In recent years, MRI has been refined so as to become an ideal, noninvasive imaging technique. With appropriate contrast media, ultra-fast MRI can now provide simultaneous information on the morphology, ductal conditions (MRCP) and blood vessels in pancreatic lesions. In the literature, this triple diagnostic measure is described as 'one-shop shopping' or 'all-in-one' MRI. In nonicteric patients, this method as a diagnostic imaging test may replace diagnostic ERCP. In a direct comparison with spiral CT, MRI in some institutions proved superior for staging of pancreatic lesions with respect to the detection rate and classification of pancreatic lesions. With the advent of MRCP, the indications for invasive ERCP have to be redefined – usually being reserved for patients requiring additional interventional endoscopic therapy (e.g. palliative drainage of the bile duct).

ERCP

This method allows the visualization of the pancreatic ductal system and is the most sensitive procedure for the demonstration of the ductal changes of chronic pancreatitis (≥90%). The anatomic and pathologic substrate on which this method is based consists of changes in the ductal system with irregular stenosis and dilatation, which are induced by periductal fibrosis and fibrotic atrophy of the pancreatic parenchyma. Depending on the stage of the disease, these changes occur initially only in the 1st- or 2nd-order side branches, but with increasing severity, these ductal changes extend to the main pancreatic duct. About 15% of patients have stone formation (calcifications) in the main pancreatic duct. In the advanced stage of the disease or as a result of a large inflammatory pancreatic tumor, there may be complete stenosis of the pancreatic duct, stimulating a differential diagnosis of cancer of the pancreas. ERCP may also be required in the differential diagnosis of advanced stenosis of the common bile duct concurrently with involvement of the pancreatic duct, since this finding is much more common in pancreatic cancer (double duct sign). The segmental form of chronic pancreatitis also needs to be differentiated from pancreatic

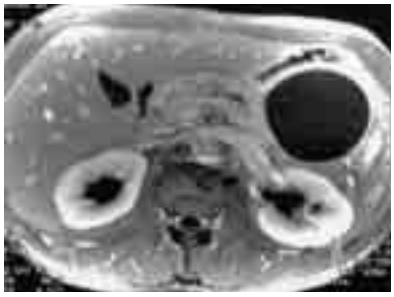
Inflammatory Tumor in the Head of the Pancreas

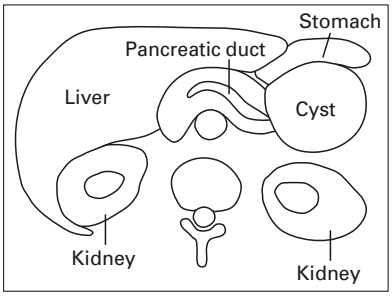




CT with large (inflammatory) tumor in the head of the pancreas and calcifications.

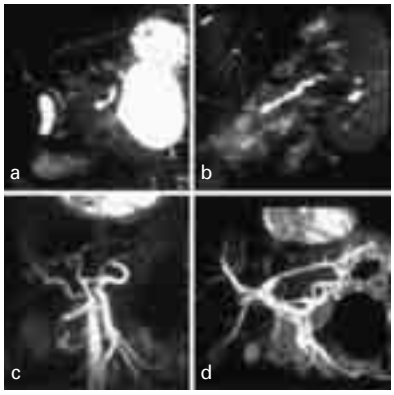
MRI Morphology





MRI. Chronic pancreatitis with inflammatory tumor in the head of the pancreas, stenosis of the pancreatic duct with resultant cyst in the tail region.

MRCP and Angiography



'All-in-one' MRI with MRCP and visualization of the blood vessels. a, b MRCP. Dilatation of the pancreatic duct and cyst in the tail region. Normal caliber of the common bile duct. c, d Normal (c) and venous (d) visualization of the vascular conditions in the pancreatic region.

carcinoma. On the basis of more isolated pathognomonic changes in the pancreatic duct in ductal adenocarcinoma and the other type of lesions found in chronic pancreatitis, it is possible, with the aid of the patient's history and clinical presentation, to distinguish correctly between the two disorders in 95% of patients.

ERCP is a justifiable procedure given appropriate preselection of patients in an attempt to identify the cause of their upper abdominal pain. In this context, in patients with suspected chronic pancreatitis, the ERCP findings in chronic pancreatitis were classified in 1984 (Cambridge classification). The drawback of this classification is, however, that the extent of the ductal changes does not correlate with the degree of impairment of the organ. Because of this drawback, a classification was proposed that takes into account only the morphologic changes and defines various types of chronic pancreatitis, including the sites and presence of obstructive changes.

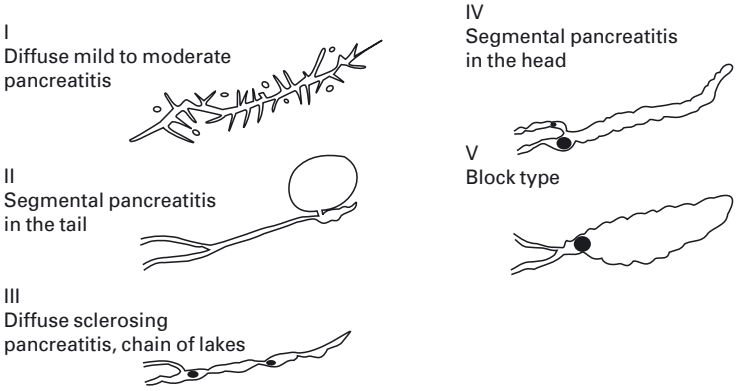
Ductal changes of mild degree (stages 1–2) occur in the normal elderly even without relevant disease, thus false-positive findings may occur.

When considering ERCP, it should not be forgotten that, in contrast to the noninvasive methods, ERCP is not without potential complications. Acute pancreatitis occurs as a complication in 1–3% of patients undergoing ERCP.

Cambridge Classification (ERCP)

Main pancreatic duct	Changes in side branches	Stage
Normal	none	normal
Normal	fewer than 3	not certain
Normal (changed)	3 or more	1
Changed	more than 3	2
Changed Marked irregular dilatation 'Pearl necklace' penomenon (also called 'chain-of-lakes') Discontinuous duct Cystic necrotic cavities	more than 3	3

Morphologic Classification



Ductal Dilatation

ERCP of stage 3 chronic pancreatitis.

Tests of Pancreatic Function

One should distinguish between exocrine and endocrine function tests. The benefit of a test for exocrine function is that it indicates the presence of chronic pancreatitis at a stage when loss of function has not yet manifested itself clinically. The various tests, however, differ markedly from each other in their sensitivity.

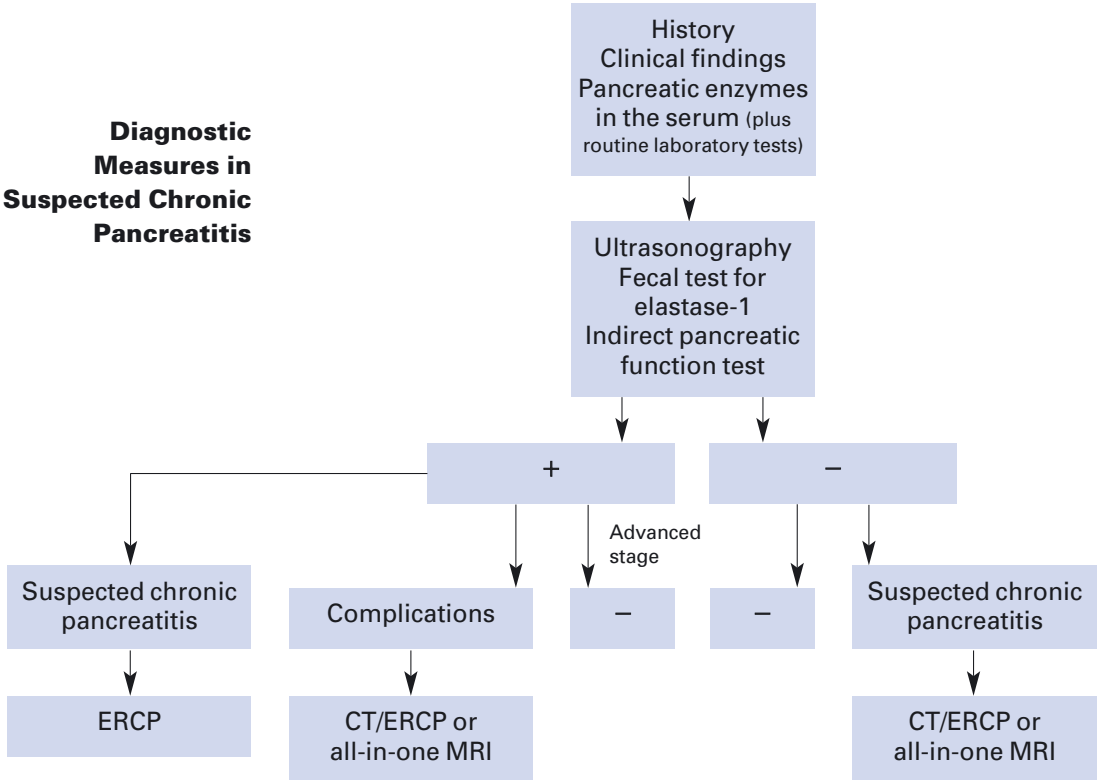
Exocrine pancreatic function tests can be a very useful complement to the imaging procedures since they provide an insight into the stage of the disease and can convey information about the planning of treatment. The most sensitive and most specific test is the invasive method of intubation and placement of a duodenal tube. Stimulation with secretin and cerulein or CCK induces maximum secretion by the gland. The secretory capacity of the exocrine pancreas under these conditions is an early indicator of the presence of chronic pancreatitis. Most hospitals have abandoned this procedure because of the discomfort to the patients as well as the cost. As an alternative, oral pancreatic function tests have become of much more interest. The pancreolauryl test (PLT) is as follows: the patient is given a test meal containing a specific substrate for the pancreatic enzyme cholesterol esterase in form of fluorescein dilaurate. Depending on the amount of this specific enzyme secreted, free fluorescein released from the fluorescein dilaurate can be measured in the blood or urine. This process allows recognition of chronic pancreatitis of moderate or severe damage if more than 50% of the gland is affected by the disease process. The serum method has proved the most reliable variant of the PLT. In this test, the fluorescein concentration is measured in the blood at time 0, and then at 30-minute intervals for a period of 180 min after ingestion of the test meal and stimulation with secretin (1 U/kg body weight) and metoclopramide (10 mg i.v.). A new fecal test found to be helpful is the determination of the elastase-1 in the feces. This method has a higher diagnostic accuracy than measurement of chymotrypsin in the feces.

Determination of pancreatic enzyme levels in the blood (amylase, lipase) is always included whenever chronic pancreatitis is suspected, but the sensitivity of these tests is extremely low. The pancreas-specific levels of these enzymes in the blood are not reduced until pancreatic insufficiency reaches an advanced stage and is associated with steatorrhea. Ironically, an increase in the levels in conjunction with clinical symptoms of disease activity (inflammation) or even without them may indicate the presence of chronic pancreatitis. Determination of the serum enzymes serves as a means of monitoring the course of the disease and can, in particular, indicate a progressive loss of parenchyma. To date there are no biochemical parameters that, as in acute pancreatitis, are of prognostic relevance. Isolated studies that investigated the measurement of procollagen peptide 3, a marker of fibrosis, were able to provide only limited information on the progression of the disease process.

The determination of PP after secretin or CCK stimulation has not proven to be of use in the diagnosis of chronic pancreatitis.

Routine clinical tests that are useful are fasting and postprandial blood sugar concentrations, or an oral glucose tolerance test with determination of the insulin and C-peptide levels.

Diagnostic Measures in Suspected Chronic Pancreatitis



Pancreatic Function Tests

Exocrine function		Sensitivity %	Specificity %
Intubation test	Secretin Secretin-cholecystokinin Secretin-cerulein (Takus)	80–90	>90
	Lundh test meal	70–90	>80
Oral function tests	Pancreolauryl test	70–85	75
	NBT-PABA test	70–80	75
Fecal test	Fat in feces	not relevant	
	Chymotrypsin	60–80	70
	Elastase-1	80–90	80–90
Serum enzymes	Pancreatic isoamylase		
	Pancreatic lipase	30–40	>90
Endocrine function			
Fasting blood sugar Oral glucose tolerance test with determination of blood sugar, insulin and C-peptide			

Treatment

The principles of treatment in chronic pancreatitis are directed at the three major clinical manifestations, i.e. treatment of the pain, exocrine insufficiency, and endocrine insufficiency. Complications – pseudocysts, obstruction (duodenal, biliary, colonic), or splanchnic venous thrombosis – that may occur in the course of chronic pancreatitis fall into the domain of endoscopic interventional and surgical treatment.

Pain Therapy

The first step in the management of the pain of chronic pancreatitis is strict abstinence from alcohol. The next step consists of a trial of oral pancreatic enzyme preparations. The effects of exogenous pancreatic enzymes on the pancreatic pain have been claimed to be directed at a secretion-inhibiting feedback mechanism. This approach is based on the still controversial concept that high concentrations of exogenously administered pancreatic enzymes (especially proteases) lead to a reduction in the ductal hypertension in the pancreatic ductal systems and thus alleviate the pain.

The clinical success of oral pancreatic enzyme replacement for pain relief remains very controversial in the literature and, in the authors' own opinion, the response is confined to a relatively small number of patients. If the patient fails to respond, the next step involves administration of analgesics with a peripheral and/or central action.

No controlled studies are available on analgesic treatment in chronic pancreatitis. Our suggested treatment regimen includes initially the administration of an antispasmodic. If this fails to produce the desired response, we use a nonsteroidal anti-inflammatory drug in combination with an inhibitor of acid secretion. It is only if these measures fail that opiate analgesics are used. Other regimens for pain currently undergoing clinical trials (e.g. octreotide in special forms of chronic pancreatitis, COX II inhibitors) hopefully will offer other avenues of success. In pain refractory to treatment, or if the patient is dependent on opiate analogues, a surgical procedure has to be considered.

Treatment of Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency presents as steatorrhea (excretion of fat in the stool in excess of 7 g daily). This occurs only after the intrinsic enzyme secretion is reduced by >85%. Although all the pancreatic enzymes are reduced to a similar degree, the maldigestion of fats is the main clinical effect. The causes of the steatorrhea involve both the relative instability of lipase compared with the other enzymes and the lack of a good compensatory mechanism for the loss of lipase.

Consequently, when treating pancreatic exocrine insufficiency, particular attention has to be paid to adequate lipase replacement. The amount of lipase necessary for the digestion of a normal fatty meal is 20,000–40,000 IU, while substantially lower amounts of trypsin are sufficient for the digestion of protein. Other requirements of an enzyme preparation, besides an adequate lipase content, are good miscibility with ingested food and chyme, unimpaired gastric emptying, and adequate bioavailability in the upper portion of the small intestine.

Only a few enzyme preparations currently on the market (e.g. Creon®) meet these requirements. These preparations are enteric coated to

Treatment

Treatment directed at the cause

Abstinence from alcohol

Pain therapy

Abstinence from alcohol
Diet
Analgesics
Pancreatic enzyme preparations

Treatment of exocrine insufficiency

Diet
Pancreatic enzyme replacement
Vitamin replacement

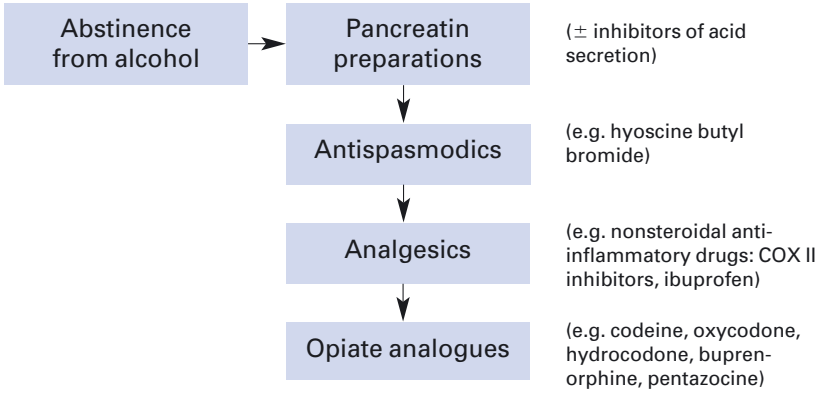
Treatment of endocrine insufficiency

Diet
Insulin

Treatment of complications

Endoscopic procedures
Surgical procedures

Pain Therapy (Staged Plan)



protect them from acid during their passage through the stomach. The pellets or microtablets released mix readily with the chyme and, because of their particle size, leave the stomach with the chyme.

The increase in pH in the duodenum to >5 is followed by the release and activity of the enzyme. The key factor for the effectiveness of the enzymes is the time of ingestion, which should be during the course of a meal.

Even with adequate enzyme replacement therapy, the treatment may be relatively ineffective in chronic pancreatitis. The most frequent cause is an inadequate rise in the pH in the duodenal lumen due to concurrent impairment of the enzyme and bicarbonate secretions. In such cases, adequate action of the enzyme preparations can be achieved by concomitant inhibition of acid secretion. If the combined treatment with inhibition of acid secretion and enzyme replacement also fails to achieve a satisfactory response, other potential causes should be excluded, such as bacterial overgrowth of the small intestine. One possibility is the use of medium-chain triglycerides (MCT) in the diet. In such situations, there may be need for parenteral administration of the fat-soluble vitamins A, D, E and K, and rarely even parenteral administration of vitamin B_{12}.

Treatment of Endocrine Pancreatic Insufficiency

Endocrine pancreatic insufficiency is initially treated by diet. The use of oral hypoglycemic agents is, if at all, only successful in the short term. When the diabetes can no longer be controlled by diet, insulin must be used. It should be borne in mind that patients with chronic pancreatitis may have an increased susceptibility to insulin, which in the case of continued alcohol consumption or after pancreatectomy (or resection of the left pancreas) can lead to serious, sometimes fatal, hypoglycemia.

The therapeutic management of patients with chronic pancreatitis will be governed by the guidelines that have been outlined briefly here. In this context, attention must be paid to the stage of the illness and the patient's individual circumstances.

Surgery

Treatment of chronic pancreatitis remains largely in the domain of specialists in internal medicine and gastroenterologists. However, the literature contains increasing information suggesting that early operative intervention can halt the progression of the disease and even improve pancreatic function in selected individuals. Due to the long-lasting illness and the complications developing in the course of chronic pancreatitis, about half the patients will ultimately undergo surgery. These findings underline the fact that, if at all possible, surgeons should be involved in the treatment plan from an early stage. Given our current knowledge of the disease, therapeutic nihilism or waiting for the disease 'to burn itself out' may not be indicated because operative treatment can help tremendously.

The surgical treatment of patients with chronic pancreatitis is designed to address three main objectives: (1) elimination of the pain syndrome, (2) treatment of disease-related complications and (3) preservation of the exocrine and especially endocrine pancreatic function.

Treatment

Diet

Limit fats to 60 g/day (with balanced amounts of proteins and carbohydrates)
Frequent small meals
Avoidance of poorly tolerated foodstuffs
In severe cases, medium-chain fatty acids
In endocrine insufficiency, diabetic diet

Pancreatic enzymes

20,000–40,000 lipase units per meal (e.g. Creon® 25,000 FIP 2–3 capsules or Panzytrat® 40,000 FIP 1–2 capsules; 25,000 FIP ≙ 8,000–10,000 lipase units)
Acid protection in patients refractory to treatment (proton pump inhibitors, e.g. 2 × 20 mg omeprazole)

Vitamins

Vitamins A, D, E, K; parenterally in patients with severe disease
B vitamins in dietary deficiency due to chronic alcoholism

Antidiabetics

Oral hypoglycemic agents are only effective temporarily
Insulin
Target blood sugar level 120–200 mg/dl (**caution:** hypoglycemia)

An inflammatory tumor develops in the head of the pancreas in 10% (United States) to about 33% (Germany, France, Europe) of patients with chronic pancreatitis. The cause of these differences between Europe and the United States remains unknown. The dominant clinical symptoms in these patients are epigastric abdominal pain and impaired digestion (maldigestion). In over 50% of patients, the chronic inflammatory tumor in the head of the pancreas causes compression of the intrapancreatic common bile duct and stenosis of Wirsung's duct in the region of the inflammatory mass. Obstruction of the duodenum and compression of the portal vein with extrahepatic portal hypertension have been described less frequently.

The surgical procedure in patients with an inflammatory mass in the head of the pancreas (complicated chronic pancreatitis) has usually been a pancreatico-duodenectomy which was performed successfully first in 1909 by Kausch and later by Whipple in the 1940s. The use of Whipple's procedure in chronic pancreatitis, though effective, is considered by some surgeons as too radical because it involves resection of about 50% of the pancreas (head and uncinate process) as well as the duodenum and bile duct. The procedure is associated with considerable morbidity. In 1972, a duodenum-preserving resection of the pancreatic head was introduced for this disease. The objective of this surgical procedure is the subtotal resection of the inflammatory tumor in the head of the pancreas while preserving the duodenum, the extrahepatic bile ducts, and a large part of the pancreatic parenchyma. Candidates for duodenum-preserving resection of the head of the pancreas are those patients who complain every week of severe, persistent epigastric and back pain and who require regular analgesic therapy. Absolute indications for surgery are development of complications, such as stenosis extending for a long section of the common bile duct with persistent jaundice and severe stenosis of the duodenum with clinically symptomatic gastric outlet obstruction. Compression of the portal vein or thrombosis in the portal venous system leading to gastric varices of itself is not an indication for operation; however, when the gastric varices bleed, splenectomy may prove necessary. In order to avoid the disadvantages of the classic Whipple's procedure, a pylorus-preserving Whipple's operation was introduced in 1978. This procedure was designed to preserve the stomach together with the pylorus and 2–4 cm of the first segment of the duodenum. The first prospective randomized clinical study that compared duodenum-preserving pancreatic head resection with the pylorus-preserving Whipple's operation showed advantages for the duodenum-preserving resection with less pain, better weight gain, better preserved glucose tolerance, and greater capacity for insulin secretion. Further advantages of this method are resection of the chronically inflamed head of the pancreas with preservation of the normal transduodenal passage of food, decompression of the extrahepatic splanchnic venous system, the bile ducts and pancreatic duct, and preservation of the duodenum. An alternative to the duodenum-preserving resection of the head of the pancreas is Frey's procedure in which a nonanatomic, subtotal 'coring out' resection of the pancreatic head is accompanied by a longitudinal pancreaticojejunostomy. This procedure is believed by some surgeons to be equally effective but technically much easier and safer.

Surgical Procedures

Drainage procedures
Ductal drainage (Puestow/Partington-Rochelle) Pseudocystojejunostomy

Resection procedures
Segmental resections (e.g. resection of the tail of the pancreas with preservation of the spleen) Pylorus-preserving pancreatico-duodenectomy Resection of the head of the pancreas with preservation of the duodenum

Surgical Objectives

Elimination of pain
Treatment of the disease-related complications
Preservation of exocrine and endocrine pancreatic function

Stones in the pancreatic duct.

The indication for resection of the left pancreas (maximum 40–60% of the distal organ) should be very carefully defined because of the postoperative risk of insulin-dependent diabetes mellitus; the disease process should be confined to the left pancreas (e.g. poststenotic obstructive chronic pancreatitis). The other patients most likely to benefit from resection of the distal pancreas are those with pancreatitis-induced splenic vein thrombosis or an inflammatory lesion located in the distal gland. The procedure may be carried out with or without splenectomy, and the stump of the pancreas may be oversewn or an anastomosis may be created via pancreaticojejunostomy with an isolated Roux-en-Y limb of the jejunum. Patients with chronic pancreatitis involving the entire gland do not do well with a distal or 'left-sided' resection.

Drainage procedures – such as a pancreaticojejunostomy by the methods of Puestow or Partington-Rochelle, or cystojejunostomy – are indicated in chronic pancreatitis associated with marked dilatation of the pancreatic duct (>8 mm) or symptomatic pancreatic pseudocysts only in the absence of extrapancreatic or peripancreatic complications (common bile duct, duodenal or vascular stenosis). The latter should be excluded by a careful preoperative investigation (ERCP, CT, MRI). These surgical procedures are also associated with lower mortality and morbidity and result in a high rate of relief from pain (60–80%).

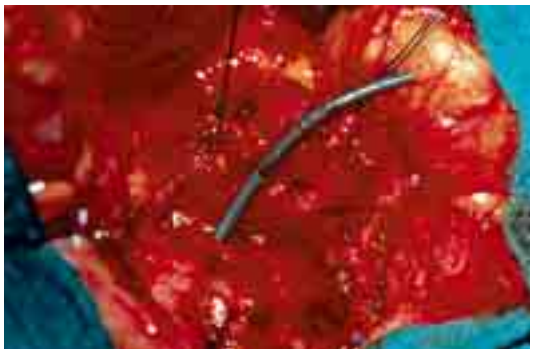
Interventional Procedures

Currently, a number of endoscopic procedures have become available for the management of chronic pancreatitis, such as the implantation of stents into the common bile duct and/or pancreatic duct and the internal or external drainage of pseudocysts (e.g. pseudocystogastrostomy with stent). Experience with these interventional procedures is, however, as yet limited, and they should be carried out only in the context of clinical studies in specialist centers. There have been very few good studies of endoscopic procedures in chronic pancreatitis (morbidity and mortality in large clinical series). The endoscopic treatment modalities are used according to the classification of the severity grades, and in this context, according to the individual anatomy of the pancreatic and common bile ducts. Impacted or distal gallstones (pancreaticolithiasis) can be treated by extracorporeal shock wave lithotripsy (ESWL) and endoscopic recovery of the fragments after papillotomy, and strictures of the pancreatic duct can be bridged by a plastic stent. This type of treatment is, as a rule, temporary but can in special circumstances and by gifted interventional endoscopists serve to avoid or delay surgery in chronic pancreatitis. The indications for endoscopic interventional treatment in chronic pancreatitis will have to be determined in future studies because there is no consensus in the literature. In connection with endoscopic interventional access, the risk of missing a malignant tumor must always be borne in mind. The problems associated with long-term stenting include, besides the risk of recurrent occlusion, a persistent inflammatory foreign-body reaction which may substantially complicate a subsequent operation.

Endoscopic/ Interventional Procedures

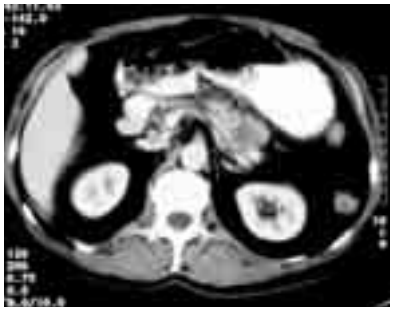
Drainage of the pancreatic/bile duct
ESWL Papillotomy Stenting of strictures

Treatment of complications
Pseudocystoenterostomy with stents



Intraoperative site after stenting of the pancreatic duct.

Obstructive Chronic Pancreatitis



Chronic pancreatitis of the tail of the pancreas following necrotizing pancreatitis.

ERCP showing occlusion of the pancreatic duct in the region of the neck of the pancreas (same patient; arrow).

Neoplasms of the Pancreas

Case 1

Male, 72, married, 2 children, teacher

History

Four weeks previously, the patient noticed his urine was becoming increasingly brown in color. Two weeks later, his wife found that he had icteric sclerae. The patient finally consulted his doctor because of excruciating pruritus. No weight loss.

Findings

Marked jaundice and multiple skin scratch marks. His abdomen was soft, and a round palpable mass could easily be felt in the right upper abdomen in the region of the gallbladder (Courvoisier's sign).

Body weight 81 kg (178 lb), height 178 cm (5 ft 10 in).
Body temperature 36.5° C (rectal), heart rate 72/min, blood pressure 145/80 mm Hg.
Laboratory Parameters: Hemoglobin 11.8 g/dl, leukocytes 7.8 × 10^9/l, AST 80 U/l, ALT 64 U/l, alkaline phosphatase 718 U/l, γ-GT 365 U/l, bilirubin 158 mg/dl, INR 1.3.

Ultrasonography

On ultrasonography, there was a dilated gallbladder with dilatation of intra- and extrahepatic bile ducts. No stones in the gallbladder or any space-occupying lesion could be seen. The pancreatic duct was diffusely dilated.

CT with Contrast Medium

CT showed dilatation of the intrahepatic bile ducts with the hepatic parenchyma of normal size and density. The gallbladder was dilated as was the common bile duct (1.4 cm) all the way distally (intrapancreatically) down to near the papilla. There was a suspicion of mass close to the papilla without evidence of metastases.

ERCP

The papilla of Vater was distended and a mass 1.5 cm in diameter was found at the papilla. Using contrast medium the common bile duct was dilated to 1.4 cm but without stones; there was stenosis in the region of the papilla. The pancreatic duct was markedly dilated. A plastic stent was inserted for decompression of the bile ducts. Biopsy of the papilla showed a moderately differentiated adenocarcinoma.

Diagnosis

Periampullary carcinoma (papilla).

Management

Preoperative evaluation for surgery.

Course

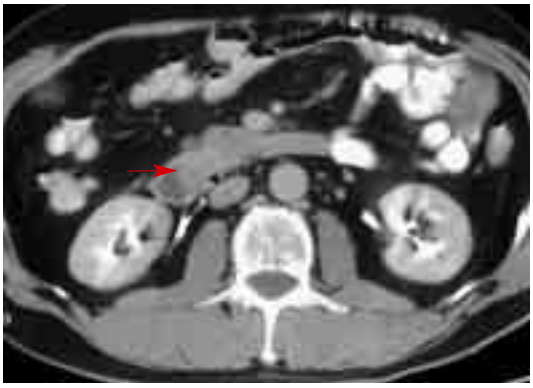
Preoperative cardiopulmonary risk assessment. Therapy with vitamin K. Laparotomy with removal of the neoplasm via a pylorus-preserving pancreaticoduodenectomy. Final histology: periampullary carcinoma, moderately differentiated, UICC stage $T_2N_0M_0$. Discharged from hospital after 3 weeks in good condition on regular diet.

Prognosis

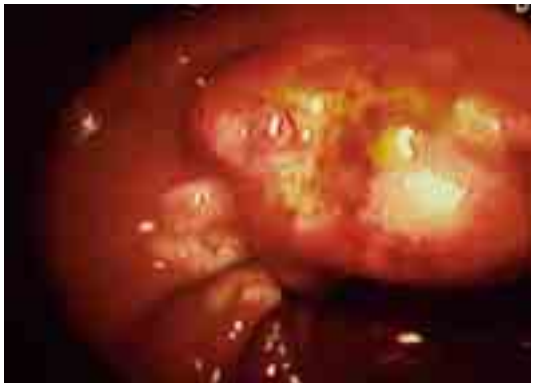
5-year survival of 30–40%.

Case Record

History	4-week history of brown discoloration of urine and increasing jaundice with pruritus
Diagnosis	Periampullary carcinoma (papilla)
Findings	Painless obstructive jaundice; palpable gallbladder (Courvoisier's sign)
Laboratory results	Alkaline phosphatase 718 U/l, γ-GT 365 U/l, bilirubin 158 mg/dl, INR 1.3
Ultrasonography	Dilated gallbladder and intrahepatic and extrahepatic bile ducts
CT	Suspected mass in the region of the papilla without evidence of metastases
ERCP	Papillary neoplasm 1.5 cm in diameter with dilatation of the entire biliary tree; pancreatic duct dilated; insertion of a plastic endoprosthesis (stent); biopsy of the papilla (adenocarcinoma)
Treatment	Pylorus-preserving pancreaticoduodenectomy, lymph node dissection
Prognosis	Stage $T_2N_0M_0$; 5-year survival of 30–40%



CT. Mass with uptake of contrast medium (arrow) in the region of the papilla.



Diagnosis of a papillary neoplasm on endoscopy.

Case 2

Nonobese female, 64, single, secretary

History

The patient had a 10-month history of atypical upper abdominal pain. Five months previously, her doctor had diagnosed insulin-dependent diabetes. She had also had severe upper back pain for 2 months. In the previous 3 months, she lost 8 kg in weight.

Findings

Signs of acute weight loss and malnutrition. The patient was pale, with epigastric pain radiating to both flanks. Her liver was coarse, nodular and enlarged. Ascites was suspected. A questionable mass in the left half of the abdomen, moderately tender, palpable.

Body weight 48 kg (105 lb), height 158 cm (5 ft 2 in).
Body temperature 36.4° C (rectal), heart rate 64/min, blood pressure 110/75 mm Hg.
Laboratory Parameters: Hemoglobin 8.5 g/dl, leukocytes 9.5 × 10^9/l, AST 35 U/l, ALT 28 U/l, alkaline phosphatase 211 U/l, bilirubin 1.1 mg/dl, creatinine 0.9 mg/dl, CA 19-9 7,900 kU/l (normal <22 kU/l).

Ultrasonography

Over 2 liters of free intra-abdominal fluid (ascites). Liver with multiple round foci in both lobes (suspicion of metastases). Body of pancreas showed a 4 × 5 cm mass with signs of infiltration posteriorly (retroperitoneum).

Fine Needle Aspiration Biopsy of the Liver

Poorly differentiated adenocarcinoma compatible with pancreatic carcinoma as the primary site.

Cytology of the Ascites Fluid

Malignant cells of adenocarcinoma type.

Diagnosis

Metastatic carcinoma of the body of the pancreas.

Management

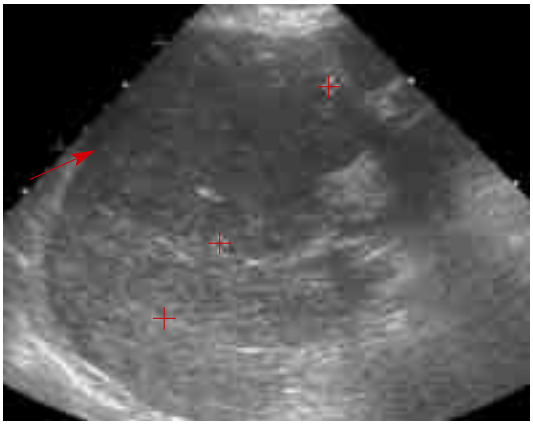
Conservative (analgesia, no hospitalization). An attempt at palliative chemotherapy was declined by the patient.

Course

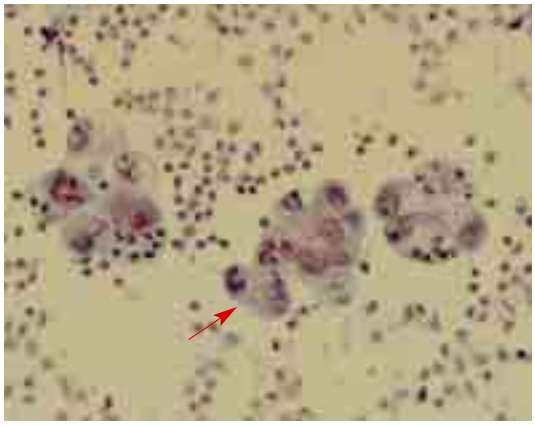
Fatal outcome 4 weeks after diagnosis: cachexia, anorexia, terminal narcotic dependence.

Case Record

History	Atypical upper abdominal pain for 10 months, weight loss of 8 kg, insulin-dependent diabetes mellitus of recent onset, increasing back pain
Diagnosis	Metastatic carcinoma of the body of the pancreas
Findings	Acute weight loss and malnutrition, ascites, mass in the left upper half of the abdomen
Laboratory results	Hb 8,5 g/dl, CA 19-9 7,900 kU/l
Ultrasound	Marked ascites, multiple round liver foci, mass in the body of the pancreas with infiltration retroperitoneally, fine needle aspiration cytology of one liver focus and cytology of the ascites fluid
Treatment	Symptomatic, graded narcotic analgesia
Course	Death 4 weeks after the diagnosis



Ultrasonography with multiple liver masses (+) and ascites (arrow).



Cytology of the ascites shows malignant cells (arrow).

Case 3

Female, 44, married, 1 child, self-employed businesswoman

History

Recurrent brief episodes of loss of consciousness for 3 years. Epilepsy was suspected and she had been on appropriate drug treatment for 2.5 years. During this time, there was a constant increase in weight of 11 kg with repeated bouts of vomiting. Admission to hospital at the request of the neurologist to investigate possible hypoglycemia.

Findings

Overweight female patient in good general condition, abdomen unremarkable.

Body weight 85 kg (187 lb), height 164 cm (5 ft 5 in).
Body temperature 36.0° C (rectal), heart rate 68/min, blood pressure 160/95 mm Hg.
Laboratory Parameters: Hemoglobin 14.5 g/dl, leukocytes 6.3 × 10^9/l, AST 23 U/l, ALT 20 U/l, alkaline phosphatase 111 U/l, bilirubin 0.9 mg/dl, creatinine 0.9 mg/dl, blood glucose 56 mg/dl.

Ultrasonography

Normal, unremarkable findings in the upper abdomen.

CT with Contrast Medium

At the transition between body and tail of the pancreas, a round 1-cm mass with uptake of contrast medium, from its appearance no suspicion of malignancy, no indications of lymph node or liver metastases.

Prolonged Fasting Test

After 7 h, plasma glucose was 56 and 38 mg/dl and neurologic symptoms with dizziness and malaise appeared; the test was stopped. Laboratory results showed hyperinsulism; the diagnosis of insulinoma was made.

Management

Hospitalization for explorative laparotomy for surgical removal of the pancreatic insulinoma.

Course

Laparotomy with intraoperative ultrasonography of the pancreas. Evidence of a 1-cm mass in the tail of the pancreas. The mass was enucleated. Discharge from hospital on the 11th day postoperatively, with normal blood sugar values.

Histology

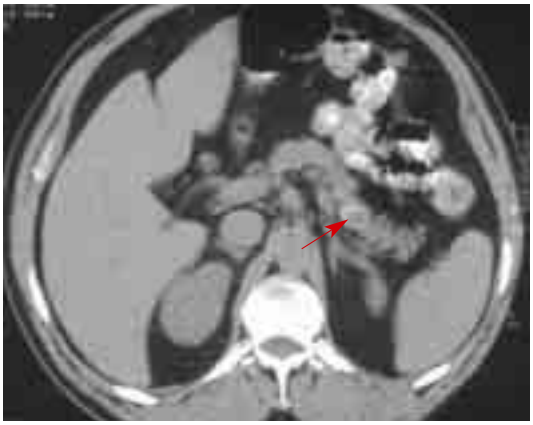
Endocrine islet cell neoplasm of the pancreas. Immunohistochemical evidence of insulin-storing cells.

Prognosis

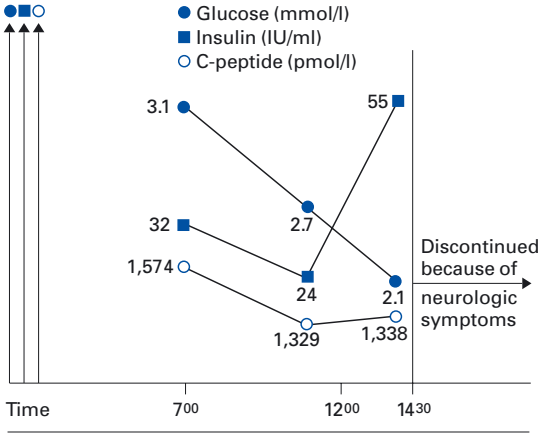
Patient is cured, because ~95% of insulinomas occur as a single neoplasm and are benign in up to 90% of patients.

Case Record

History	Recurrent brief loss of consciousness, initial suspicion of epilepsy, weight increase of 11 kg, in view of suspected hypoglycemia further investigation
Diagnosis	Insulinoma in the tail of the pancreas
Findings	Unremarkable
Laboratory results	Blood glucose 56 mg/dl, otherwise normal routine laboratory findings
Ultrasonography	Unremarkable
CT	At the transition between the tail and body of the pancreas an approximately 1-cm-large mass with uptake of contrast medium
Prolonged fasting test	Hypoglycemia with increased insulin and C-peptide levels
Treatment	Enucleation of mass (insulinoma); on intra-operative ultrasonography, no other masses noted
Prognosis	Insulinomas are benign and unicentric in 90% of patients, so she should be cured



Mass in the body/tail of the pancreas (arrow).



Fasting test.

An Atypical Case

Female, 56, married, housewife

History

One-year history of recurrent abdominal pain with diarrhea. In the previous 10 months, marked weight loss of 11 kg. Cholecystectomy performed previously in 1977; vaginal hysterectomy in 1992. Ultrasonography showed a mass in the pancreas and the patient was admitted to hospital for further investigation and treatment.

Findings

Unremarkable general and nutritional state. Tenderness in the epigastrium. Palpable mass in the upper abdomen.

Body weight 76 kg (167 lb), height 164 cm (5 ft 5 in).
Body temperature 37° C (rectal), heart rate 72/min, blood pressure 120/75 mm Hg.
Laboratory Parameters: Routine laboratory examinations showed all results to be normal, including tumor markers, CEA and CA 19-9; abnormal OGTT with 2-hour value of 274 mg/dl.

All-in-One MRI

Magnetic resonance: Large cystic, lobulated pancreatic mass involving the entire pancreas 10 × 4 cm in size. No suggestion of liver metastases.

MRCP: Occlusion of the pancreatic duct in body of the pancreas 3–4 cm proximal to the papilla of Vater. Normal extra- and intrahepatic bile duct system.

Diagnosis

Suspected cystadenocarcinoma of the pancreas.

Treatment

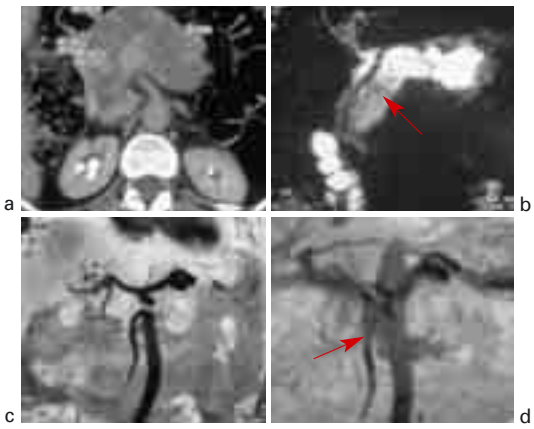
A total pancreaticoduodenectomy was performed with preservation of the pylorus, extended regional lymph node dissection, splenectomy, and segmental resection of the portal vein with end-to-end anastomosis. Final histology: serous cystadenoma of the pancreas.

Course

Two and a half years later, a large 4-cm cystic lesion was noted in liver segments II/III and a further lesion in liver segment VI. No evidence of local recurrence. Further operation with bisegmentectomy of II/III and non-anatomic liver resection of segment VI. Histology: metastasis of the serous cystadenocarcinoma. One year later, as before, free of recurrence.

Case Record

History	Recurrent abdominal symptoms of 1-year diarrhea, weight loss of 11 kg
Diagnosis	Suspected cystadenocarcinoma of the pancreas
Findings	Good general and nutritional state, tender epigastric mass
Laboratory results	–
Magnetic resonance	Large, cystic tumor occupying the entire pancreas
MRCP	Occlusion of the pancreatic duct in the region of the body of the pancreas
Treatment	Total pancreaticoduodenectomy with preservation of the pylorus 2.5 years later, liver resection for metastatic serous cystadenocarcinoma of the pancreas
Prognosis	Unknown prognosis (no data, *very* rare occurrence)



MRI (a), MRCP (b) and MR-angio (c: arterial; d: venous). Cystic lobulated pancreatic mass, occlusion of the pancreatic duct (arrow) and suspected infiltration of the portal vein (arrow).

Definition and Classification

Our recognition of neoplasms of the pancreas has markedly increased in frequency in the last 60 years. They account for nearly one third of all pancreatic diseases. The increase in neoplastic pancreatic diseases is related in part to the fact that human beings live longer – neoplasms of the pancreas are diseases of the elderly – but also because more are detected due to improved diagnostic techniques. The most frequent neoplasm of the pancreas is pancreatic ductal adenocarcinoma (approximately 80% of all neoplasms), followed by periampullary or ampullary carcinoma, and endocrine neoplasms of the pancreas. These three principal neoplasms will be discussed below in accordance with their clinical importance.

Pancreatic neoplasms are divided according to the WHO classification into benign and malignant neoplasms arising from the exocrine or endocrine portion of the pancreas.

Benign Neoplasms

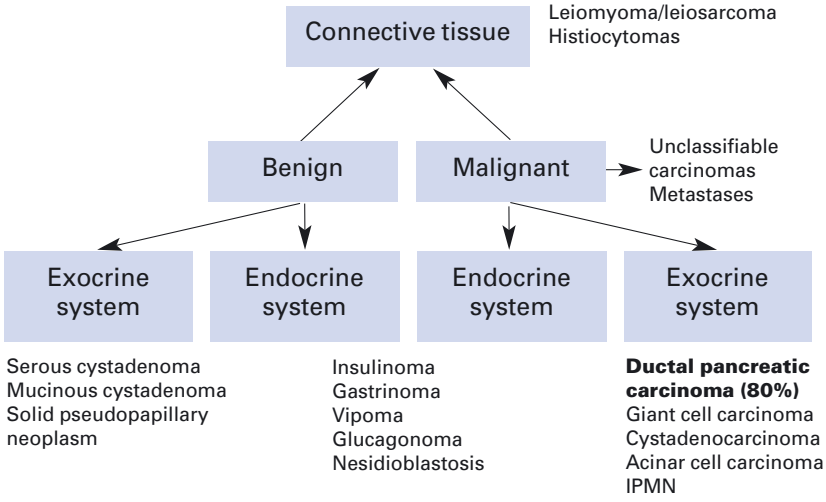
Benign pancreatic neoplasms are rare. Most arise from the endocrine system. Benign exocrine neoplasms, the next most frequent, are benign cystic neoplasms, such as serous cystadenoma, mucinous cystadenoma, or the rare solid pseudopapillary neoplasm of the pancreas. To date, a few hundred of these benign exocrine neoplasms have been described in the world literature. They may occur in all parts of the pancreas, with a predilection for the body and tail of the pancreas. Women between 40 and 60 years old are most often affected. The clinical features of benign exocrine neoplasms of the pancreas usually includes atypical upper abdominal pain, which sometimes radiates to the back or they may be totally asymptomatic. The slow course and growth characterized by the mass effect of these neoplasms account for the atypical symptomatology. The symptoms generally develop slowly, over a period of years, and are caused on occasion by external compression of the bile duct with jaundice or the duodenum with gastric outflow obstruction. Benign neoplasms of the pancreas should be treated surgically, usually by resection of the affected portion of the pancreas.

Malignant Neoplasms

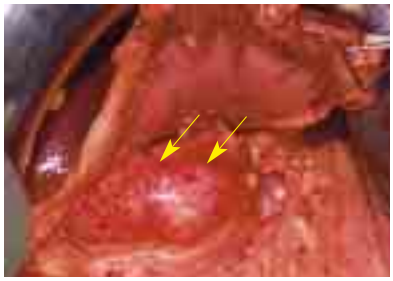
The most frequent cancer of the pancreas is ductal pancreatic carcinoma (80% of all patients). A series of rare malignant neoplasms arise from exocrine tissue (5–10%), such as giant cell carcinoma, cystadenocarcinoma, acinar cell carcinoma or the recently increasingly recognized intraductal papillary mucinous neoplasm (IPMN) of the pancreas. IPMN is an intraductally growing mucin-producing neoplasm which leads to dilatation of the pancreatic duct and is characterized histologically by papillary formation with cell atypia. Clinically, these neoplasms are usually asymptomatic, but can also present as recurrent pancreatitis or masquerade as chronic pancreatitis with pain and steatorrhea. However, in more than 30% of patients they transform into invasive carcinoma. These neoplasms are being recognized with increasing frequency and currently account for 10 to 15% of all resections for pancreatic neoplasms.

Connective tissue neoplasms, such as leiomyosarcoma or histiocytoma, as well as neurogenic neoplasms or metastases, occur extremely rarely in the pancreas.

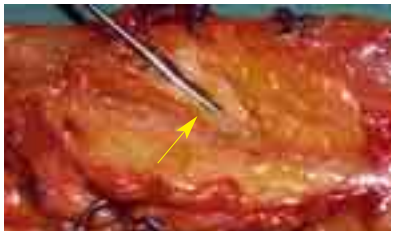
Classification



Macroscopic Preparations



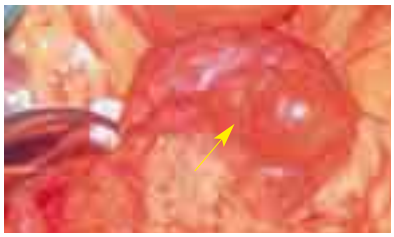
a



Surgical preparation. Carcinoma of the head of the pancreas with infiltration of the bile duct (probe).

b

Serous cystadenoma of the pancreas involving the whole pancreas (atypical case of page 132). Intraoperative site (a; arrows = neoplasm) and dissected specimen (b).



Cystadenocarcinoma. Intraoperative site with cystic space-occupying lesion (arrow) in the body of the pancreas.

Pancreatic Carcinoma

As in the past, carcinoma of the pancreas presents major diagnostic and therapeutic problems. In most patients, the diagnosis is made too late. Apart from resection in the early stages, therapeutic options are limited. Thus, the aim for the future is to be able to diagnose this neoplasm early in order to improve the extremely poor prognosis.

Epidemiology

Carcinoma of the pancreas appears to have an increasing incidence throughout the world. It is more frequent among males (male:female ratio of 1.5-2:1). In Western industrialized countries, the frequency is currently 10 cases per 100,000 inhabitants. In the United States, approximately 25,000 new cases are recorded each year, while in Germany the figure is 6,000–8,000. Carcinoma of the pancreas is the 4th most common cause of cancer-related mortality for males (after carcinoma of the bronchus, prostate and large intestine). The highest incidences, of up to 20 cases per 100,000 inhabitants, are found among African-American males, while the lowest incidences – approximately 1 case per 100,000 inhabitants – are found in India, Singapore and Kuwait.

Carcinoma of the pancreas is typically a disease of old age, with a peak incidence between the ages of 60 and 80. While the incidence in 30-year-olds is 0.1 case per 100,000 inhabitants, among 80-year-olds the incidence is about 200 cases per 100,000.

Etiology

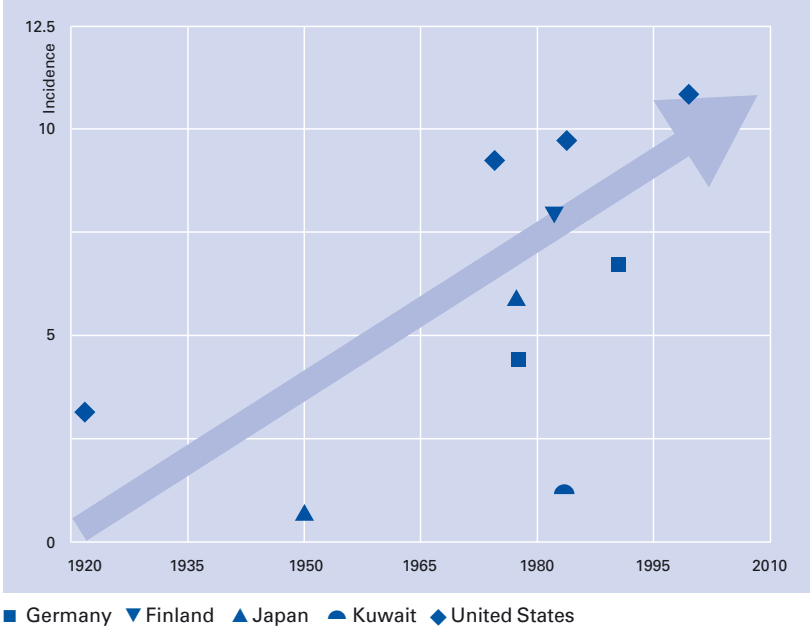
The etiology of carcinoma of the pancreas is not known. Factors that favor its occurrence include smoking and a diet with a high fat content.

No association has been shown between a high consumption of alcohol or coffee and carcinoma of the pancreas. Insulin-dependent diabetes mellitus also does not represent a risk for carcinoma of the pancreas; however, new onset of diabetes mellitus in a nonobese patient older than 40 years should alert the physician to the possibility of an underlying pancreatic cancer. In animal studies, carcinoma of the pancreas may be induced by long-term treatment with carcinogens, such as azaserine or nitrosamines. We therefore assume that these or other carcinogens are also involved in humans as cofactors in the development of carcinoma of the pancreas. This is also supported by the occurrence of this disease in advanced age.

Genetic Predisposition and Factors

Studies to date have shown that in about 10% of patients with carcinoma of the pancreas there is a genetic predisposition. Various diseases, with their known genetic alterations, have now been directly associated with the development of carcinoma of the pancreas. Hereditary pancreatitis, acquired in an autosomal dominant manner, involves a 70- to 100-fold increased risk, while long-standing chronic alcohol-induced pancreatitis shows a 5- to 15-fold increased risk of carcinoma. Patients with cystic fibrosis have a 5-fold increased risk of the occurrence of pancreatic carcinoma. Through epidemiologic studies, certain nonpancreatic diseases show an increased risk of carcinoma of the pancreas, e.g. the Peutz-Jeghers syndrome (by up to 132 times), dysplastic nevus syndrome (by 13–65 times), familial breast carcinoma (by 3.5–10 times), and familial polyposis coli (by 4.5 times).

Incidence per 100,000 Inhabitants



Carcinoma of the Pancreas: Nutritional and Toxic Risk Factors

Risk factors	Increase in risk of carcinoma, %
Smoking	14–33
High-fat diet	12–36
Carcinogens (azaserine, nitrosamine)	?
Coffee	no association

Carcinoma of the pancreas that occurs with increased frequency among family members (at least 3 first-degree relatives) involves an approximately 57-fold increased risk. The genetic cause of hereditary carcinoma of the pancreas was recently localized on the long arm of chromosome 4. The increased risk of familial pancreatic cancer may possibly be decreased by treatment with β-carotene, COX II inhibitors, or stopping smoking.

The molecular pathogenesis of carcinoma of the pancreas has been investigated intensively. Activation of the transforming oncogene K-ras and inactivation of tumor suppressor genes have been identified in pancreatic tissue and pancreatic secretions. K-ras is dominantly inherited on chromosome 12 and is believed to transform cells into malignancies. The tumor suppressor genes include p53, the best known one, which is activated in response to DNA injury and is involved in its repair. Other tumor suppressor genes are DPC4, CDKN2, BRCA-2 and SMAD4. The fact that these genes are secreted in pancreatic secretion enables them to be used potentially in molecular diagnosis and screening. The accuracy of brush cytology during ERCP with identification of K-ras or p53 is about 85% for the presence of a carcinoma of the pancreas.

This new field of research offers hope that further genes and their penetrance will be identified, and thus their clinical importance described. Specific precautions and/or treatments (prophylactic surgery, gene therapy) will then need to be established in the future.

Pathologic Anatomy

Ninety percent of all pancreatic carcinomas arise from the ductal epithelium; about 80% of all pancreatic carcinomas arise in the head of the pancreas, and 80% have already metastasized at the time of diagnosis, i.e. it is a very aggressive cancer. Particularly typical for the biology of the tumor is invasion of the intrapancreatic nerve sheaths, which also causes the characteristic back pain. Lymphatic metastases occur in two thirds of patients. In the case of hematogenous metastasis, the liver is affected in 80% of patients. Next in frequency of metastasis are the lungs and peritoneal surfaces; the adrenal glands, kidneys, pleura, and skeleton are more rarely affected. Histologically and on electron microscopy there are three grades of tumor differentiation: grade 1 is a highly differentiated carcinoma (40% of tumors), grade 2 is a moderately differentiated adenocarcinoma (approximately 50%), and grade 3 is a poorly differentiated or undifferentiated adenocarcinoma (approximately 10%).

Molecular Biology

Carcinoma of the pancreas is characterised by particularly aggressive and invasive growth, together with a poor overall survival of patients. The last 15 years have seen intensive research worldwide on the study of the tumor biology and especially the control of growth and metastases of pancreatic carcinoma. After transformation, neoplastic cells need 'growth factors', which bind to receptors on the cell surface. These factors include amongst others epidermal growth factor (EGF), transforming growth factors (TGF-α, -β) and fibroblast growth factors (BFGF), which have receptors of the same name on the tumor surface (e.g. EGF receptor).

In terms of tumor biology, malignant growth is characterised by various features: (a) auton-

Pathologic Anatomy

Histologic preparation. Carcinoma of the pancreas (arrow) with infiltration of nerves.

Carcinoma of the Pancreas: Genetic Predisposition

Disease	Gene	Remarks	Increase in risk of carcinoma, %
Chronic pancreatitis	disease-modulating genes SPINK1, CFTR (others)	genetic and environmental factors (alcohol)	5–15
Hereditary pancreatitis	PRSS1 (approx. 70%)	autosomal dominant, point mutations, approx. 80% penetrance	70–100
Familial carcinoma of the pancreas	4q32–34	autosomal dominant, reduced penetrance	56
Cystic fibrosis	CFTR	autosomal recessive, point mutations, mutations in 5%	approx. 5
Familial atypical multiple-mole melanoma	CDKN2A CDK4	autosomal dominant, point mutations	13–65
Peutz-Jeghers syndrome	STK11/LKB1	autosomal dominant	≤132
Familial breast carcinoma	BRACA2	autosomal dominant, reduced penetrance, point mutations	3.5–10
Familial polyposis coli	APC 8 (approx. 80%)	autosomal dominant, point mutations	4.5

omous control of growth (EGF, FGFs), (b) resistance of neoplastic cells to growth inhibition (TGF-β), (c) resistance to apoptosis, e.g., pancreatic carcinoma cells have developed intracellular mechanisms that circumvent pro-grammed cell death (EGF, IGF = insulin-like growth factor), (d) induction of neoangiogenesis as an important precondition for tumor growth through growth factors such as vascular epithelial growth factor (VEGF) or fibroblast growth factor (FGF-2), and (e) invasion and metastasis, in order to penetrate the surrounding tissue and to achieve deposition of tumor cells from the primary tumor with the formation of distant metastases. For invasion, growth factors such as TGF-βs, nerve growth factor (NGF) and hepatocyte growth factor (HGF) play an important role, while for metastases, a change in the expression and function of cell adhesion systems (e.g. the loss of E-cadherin expression) is important. Other important molecules that play a leading role in metastasis are proteases, e.g. matrix metalloproteinases or the urokinase/plasminogen system. Deregulated expression of these enzymes leads to the neoplastic cells breaking down the extracellular matrix and being able to better penetrate the surrounding tissue. The positive effects found in animals with the use of matrix metalloproteinase inhibitors have to date not been realized as yet in patients.

In pancreatic carcinoma, the receptors on the cell surface are, in most cases, increased in number and the cell itself also produces greater quantities of growth factors. This type of transformation stimulates further growth with invasion and metastasis, thereby negatively influencing the prognosis of patients. Immunohistochemical studies in human pancreatic carcinoma tissue showed that patients who overexpressed both the EGF receptor and EGF and/or TGF-α had a significantly shorter postoperative survival than patients who did not have simultaneous overexpression of the receptor and ligand. TGF-βs, in contrast, inhibit the growth of epithelial cells, influence the structure of the extracellular matrix, stimulate angiogenesis, and furthermore have an immunosuppressant effect. Overexpression of TGF-βs in pancreatic carcinoma cells is accompanied by more aggressive tumor growth, which is associated with a markedly reduced survival.

These different families of growth factors and receptors interact with each other in a complex manner, the exact description of which is beyond the scope of this book. In the future, new techniques in molecular biology could, however, result in new treatment strategies for curative and/or palliative treatment of carcinoma of the pancreas, as well as allowing much more sensitive and specific diagnostic techniques. Therapeutic options include, for example, the inhibition of individual components of the EGF family (e.g., tyrosine kinase inhibitors for blockade of the EGF receptor) or other growth factors and their receptors.

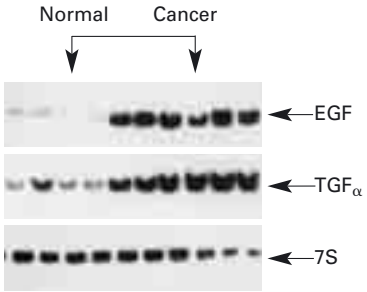
Staging

From the clinical standpoint, it is important that all neoplastic diseases are staged uniformly with regard to their local and distant extent. In accordance with an international agreement (UICC, 1993), the TNM system is now used clinically to classify and describe pancreatic cancer. The T category describes primarily the size and local extension of the primary tumor. For carcinoma of the pancreas, the categories range from T_0 (no identifiable primary site) to T_4 (tumor

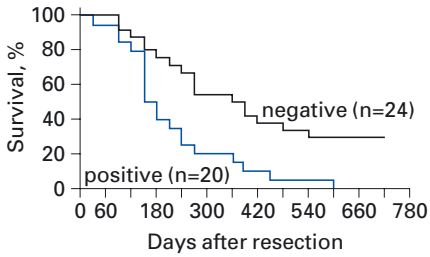
Basic Characteristics of Malignant Growth

Characteristics of malignant growth	Pancreatic carcinoma
Autonomous growth control	Increased expression of EGF, FGF, PDGF, IGF and their receptors
Resistance to growth inhibitors	Increased expression of TGF-βs and their receptors, but Smad4 mutations, Smad-6 and Smad-7 hyperexpression
Resistance to apoptosis	Increased expression of EGF, IGF and their receptors
Angiogenesis	Increased expression of VEGF, FGF-2 and their receptors
Invasion and metastases	Increased expression of HGF, TGF-βs, NGF and their receptors

Molecular Biology



Increased expression of EGF and TGF_{α} in pancreatic carcinoma.



Reduced survival in patients with increased density of growth factors (EGF, EGFR, TGF_{α}).

spreads directly into stomach, spleen, colon or other neighboring organs). The second category is the N classification. N signifies regional lymph nodes. In the case of carcinoma of the pancreas, we distinguish between N_0 (no regional lymph nodes affected) and N_1 (regional lymph node metastases). The third category is the M category, which describes the presence or absence of distant metastases. M_0 means 'no distant metastases', M_1 means distant metastases in lung, liver, etc. By means of the TNM criteria, carcinoma of the pancreas can be classified into 4 stages, which, in ascending order, are associated with an increasingly poorer prognosis.

Clinical Features

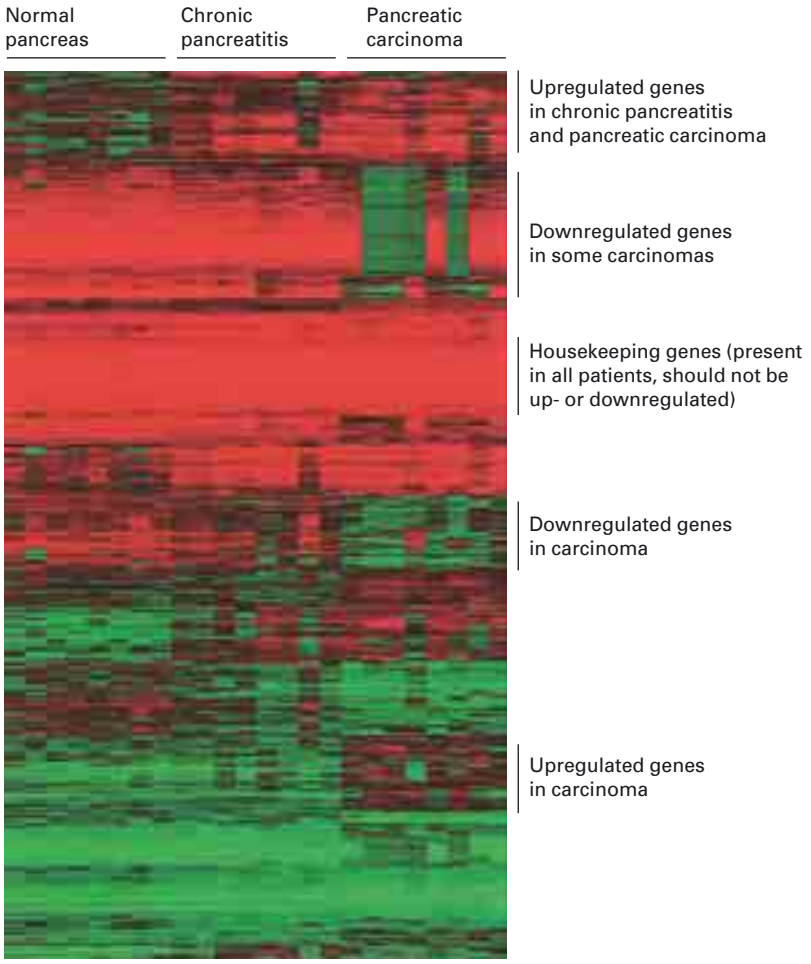
In most carcinomas of the pancreas, the diagnosis is too late for curative therapy. This is due to the atypical symptoms that develop, sometimes over months. The classic symptom complex of carcinoma of the pancreas includes upper abdominal pain radiating through to the back, loss of weight of approximately 1–2 kg per month, and progressive jaundice with carcinomas that arise in the head of the pancreas. Only one fifth of all pancreatic cancers arise in the body and tail of the pancreas. These carcinomas in the left portion of the pancreas do not cause bile duct obstruction and therefore become symptomatic even later in the course of the disease than carcinomas of the body of the pancreas. Clinical experience shows that carcinomas of the body and tail of the pancreas are generally not curable. Compared with the above symptoms, a palpable mass, hepatomegaly and Courvoisier's sign occur less frequently.

The occurrence of carcinoma of the pancreas is frequently associated with the recent onset of diabetes mellitus. We suspect that this diabetes is triggered by certain peptides produced by exocrine neoplasms of the pancreas such as islet-associated polypeptide (IAPP). Especially worrisome is the new onset of diabetes mellitus in a non-obese individual.

Diagnosis

The diagnosis of carcinoma of the pancreas often begins with an ultrasonographic examination of the abdomen; other pancreatologists maintain that CT is a better initial test in patients strongly suspected of having a pancreatic cancer. This approach is suggested because patients with pancreatic cancer diagnosed by ultrasonography will eventually undergo a CT anyway for staging. Ultrasonography and especially CT provide valuable information about the presence of a mass in the pancreas and extrahepatic biliary obstruction which differentiates a pancreatic cancer from hepatitis in the jaundiced patient. In addition, the neighboring organs, especially the liver, can be examined for metastases. Eighty percent of all patients with carcinoma of the pancreas have metastasis at the time of diagnosis (lymph nodes, liver) so that it is not unusual to find multiple liver metastases at the time of the initial diagnosis. Imaging is also essential because, if liver metastases are present, surgical measures are no longer relevant. In this situation, obstructive jaundice caused by the mass can be palliated by an endoscopic measure (insertion of an endoprosthesis or stent). Questionable lesions resembling metastases and the primary neoplasm can be biopsied using fine-needle aspiration cytology as part of the initial investigation. In the presence of metastases, fineneedle aspiration is necessary to estab-

Modern Techniques of Gene Analysis



Example of DNA microassay. Simultaneous analysis of 40,000–50,000 genes

lish the diagnosis and begin chemotherapy or radiation therapy. If there is no evidence of metastases, the lesion looks 'resectable', and the patient is a candidate for resection (good medical health), fine-needle aspiration should not be undertaken in view of the risk of dissemination of tumor cells and because, if the aspiration cytology is 'negative', it does not rule out a neoplasm because the false negative rate is 20 to 40%.

If the imaging procedure cannot confirm the diagnosis, the next investigation is ERCP. Direct imaging of the biliary system and pancreatic ductal system enables the diagnosis of 'carcinoma of the pancreas' to be made in 90% of patients. The double-duct sign is almost pathognomonic, i.e. simultaneous stenosis of the pancreatic duct and the common bile duct with distal dilatation of both ducts signifying chronic obstruction. In severe obstructive jaundice (bilirubin above 15 mg/dl), an endoprosthesis (plastic stent) may be introduced via a transampullary approach into the common bile duct as part of the ERCP after prior papillotomy. This leads to a decrease in the jaundice with subsequent improvement in the general condition of the patient. A plastic endoprosthesis does not impede the surgeon during operative therapy for carcinoma of the pancreas. More recent studies have shown no advantage of routine preoperative stenting: on the other hand, the rate of infective complications is increased.

On laboratory investigations, three quarters of patients are found to have an increased alkaline phosphatase and bilirubin as well as anemia. Unlike other malignant diseases, in carcinoma of the pancreas, the diagnosis may be made preoperatively via the tumor marker CA 19-9 which has a sensitivity of 70–80% and a specificity of about 80–90%. CA 19-9 levels above 100 kU/l (normal value <22 kU/l) are strongly suggestive of carcinoma of the pancreas, especially if there is no jaundice.

Generally speaking, the combination of ultrasonography or CT, ERCP and serum CA 19-9 levels allows the diagnosis of carcinoma of the pancreas to be made. In patients who have distant metastases (liver and/or lung), the diagnostic workup is completed with these three investigations. All other patients with carcinoma of the pancreas are potential candidates for surgery. The next step is a contrast medium-enhanced spiral three phase CT of the abdomen for staging (if not already done). The local extent of the tumor may also be determined. CT allows the surgeon to determine whether retroperitoneal involvement of the important peripancreatic blood vessels is present, which would preclude curative resection. Infiltration of the large arteries in proximity to the pancreas (celiac trunk, common hepatic artery, superior mesenteric artery) is a contraindication to operative therapy. Infiltration of the peripancreatic veins (splenic vein, superior mesenteric vein, portal vein) is not necessarily a contraindication to radical surgical measures but complicates surgical resection. Similarly, peripancreatic lymph node metastases are also not necessarily contraindications to operative therapy. In carcinoma of the pancreas, as part of radical surgical therapy, lymph node dissection is performed to remove all the regional lymph node metastases. Like ultrasonography, CT of course offers the possibility to assess the extrapancreatic organs. A search should be made during this preoperative staging for the presence of liver metastases. Nuclear mag-

TNM Classification (UICC 1997)

T classification

T_X	primary neoplasm cannot be assessed
T_0	no indication of primary neoplasm
T_{is}	carcinoma in situ
T_1	neoplasm limited to the pancreas, ≤2 cm in its largest dimension
T_2	neoplasm limited to the pancreas, >2 cm in its largest dimension
T_3	neoplasm extends directly into the duodenum, common bile duct, and/or peripancreatic tissue
T_4	neoplasm extends directly into the stomach, spleen, colon and/or neighboring large vessels

N classification

N_X	regional lymph nodes cannot be assessed
N_0	no regional lymph node metastases
N_1	regional lymph node metastases
N_{1a}	metastases in one single regional lymph node
N_{1b}	metastases is several regional lymph nodes

M classification

M_X	distant metastases cannot be assessed
M_0	no distant metastases
M_1	distant metastases

UICC Staging (1997) and Prognosis

Stage	TNM system			Median survival	
				months	2-year survival rate, %
Stage 0	T_{is}	N_0	M_0		
Stage I	T_1 T_2	N_0 N_0	M_0 M_0	12–18	20–35
Stage II	T_3	N_0	M_0		
Stage III	T_1 T_2 T_3	N_1 N_1 N_1	M_0 M_0 M_0	6–10	10
Stage IVA	T_4	Any N	M_0	3–6	0
Stage IVB	Any T	Any N	M_1		

netic resonance, which has been further developed, offers excellent imaging of the liver. Using ultra-rapid MRI and special contrast media, excellent imaging of the morphology of the vessels and duct may be shown, and there is no need for a combination of CT, ERCP and angiography. Using one imaging modality (CT or MRI), important questions about a pancreatic lesion may be answered.

When vascular infiltration is suspected, angiography of the celiac trunk and mesenteric circulation may be undertaken. This investigation is, however, not part of the routine preoperative staging. In rare cases when ERCP is unsuccessful, percutaneous transhepatic cholangiography (PTC) will show the hepatic extent of the bile duct obstruction and thereby may aid in diagnosis. This procedure is invasive, however, and has complications and thus is only rarely indicated.

Endoscopic ultrasonography is currently under development. The first clinical studies showed promising results; in the future this examination may play a role in the routine investigation of carcinoma of the pancreas. Positron emission tomography (PET) has been introduced recently in an attempt to differentiate carcinoma of the pancreas and chronic pancreatitis. The initial studies have suggested promising results, with 90% diagnostic accuracy in identifying carcinoma. Further studies are necessary, however, for validation because PET is also very expensive.

In the era of laparoscopic surgery, laparoscopy has undergone a renaissance in staging of intraabdominal malignancies and especially so for hepatopancreatobiliary malignancies. Staging laparoscopy may be used before surgical therapy of carcinoma of the pancreas. Using this technique, approximately 10% of patients may be spared a noncurative laparotomy, specifically in cases of intraperitoneal tumor seeding (peritoneal carcinomatosis, small liver metastases, malignant ascites). The danger of tumor cell dissemination through laparoscopy in patients with resectable tumors must be borne in mind, however.

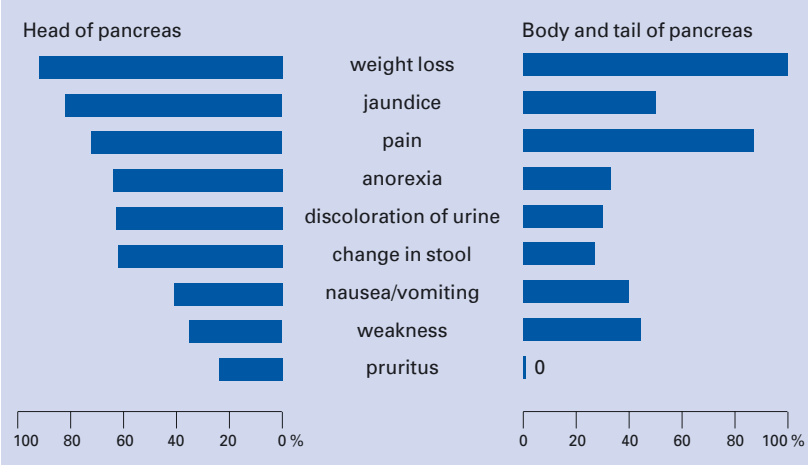
Complications

Since carcinomas of the pancreas occur predominantly in the head of the pancreas, the local growth of the neoplasm leads to obstruction of the structures in the region such as the common bile duct (jaundice) and the pancreatic duct (dilatation of the duct, rarely even acute pancreatitis). The duodenum is also involved frequently, in the form of stenosis with recurrent vomiting, but occasionally as upper gastrointestinal bleeding, when the neoplasm invades the proximal duodenum.

Approximately one third of carcinomas of the head of the pancreas lead to obstruction or involvement of the vessels. The clinical signs of extrahepatic splanchnic venous involvement/obstruction are portal hypertension (formation of ascites, esophageal or gastric varices, splenomegaly). Carcinomas of the pancreas located in the body and tail of the pancreas frequently ($\geq$60%) involve the splenic vessels. Furthermore, these neoplasms show infiltration of the retroperitoneal nerve plexus (hence pain).

In approximately 3% of all patients with carcinoma of the pancreas, the first symptom is acute pancreatitis. This is caused by obstruction of the pancreatic duct. Among clinical cases seen nowadays, the previously much described thrombophlebitis migrans in the presence of carcinoma of the pancreas is rather rare (much less than 5%).

Clinical Features



Sensitivity of Diagnostic Methods

Method	<80%	>80%
Laboratory diagnosis	CA 19-9	
Radiologic procedures	Ultrasonography CT MRI Angiography PTC	ERCP All-in-one MRI All-in-one CT
Cytology	FNA	

Differential Diagnosis

The differential diagnosis of carcinoma of the pancreas includes many other diseases of the pancreas, especially chronic pancreatitis, pancreatic cystic lesions (benign and malignant), metastatic disease, lymphoma and benign neoplasms. Often, the most difficult decision clinically is to differentiate between chronic pancreatitis and pancreatic cancer. Because as many as 15–30% of patients with pancreatic cancer have an enlarged head of the pancreas (and on occasion a dilated pancreatic duct and/or common bile duct), the differentiation may be difficult in individual patients. Usually, however, the differential diagnosis is possible via ERCP, because with chronic pancreatitis the entire pancreatic parenchyma and ductal system show characteristic signs of inflammation. For experienced clinicians, the differential diagnosis between carcinoma of the pancreas and chronic pancreatitis may be resolved in over 90% of patients; however, in the remaining 10%, preoperative differentiation is not possible. Also, one must always remember that patients with chronic pancreatitis are at increased risk of developing pancreatic cancer, which makes this topic even more difficult.

Also important for the differential diagnosis are the types of jaundice, that is, development and extent of biliary obstruction by choledocholithiasis or intrahepatic cholestasis secondary to primary hepatic dysfunction in the absence of mechanical extrahepatic biliary obstruction. In approximately two thirds of all patients with pancreatic carcinoma, symptoms in the upper abdomen and back lead to chronic gastroenterologic treatment (ulcer, dyspepsia, motility disorders) or even orthopedic treatment (degenerative and inflammatory diseases of the vertebral column). It therefore follows that patients over 60 years of age with atypical upper abdominal symptoms present for more than 2 weeks, especially radiating to the back, should undergo gastrointestinal investigation with regard to pancreatic carcinoma. Probably the best initial screening examination is either a CT or an ultrasonography.

Treatment

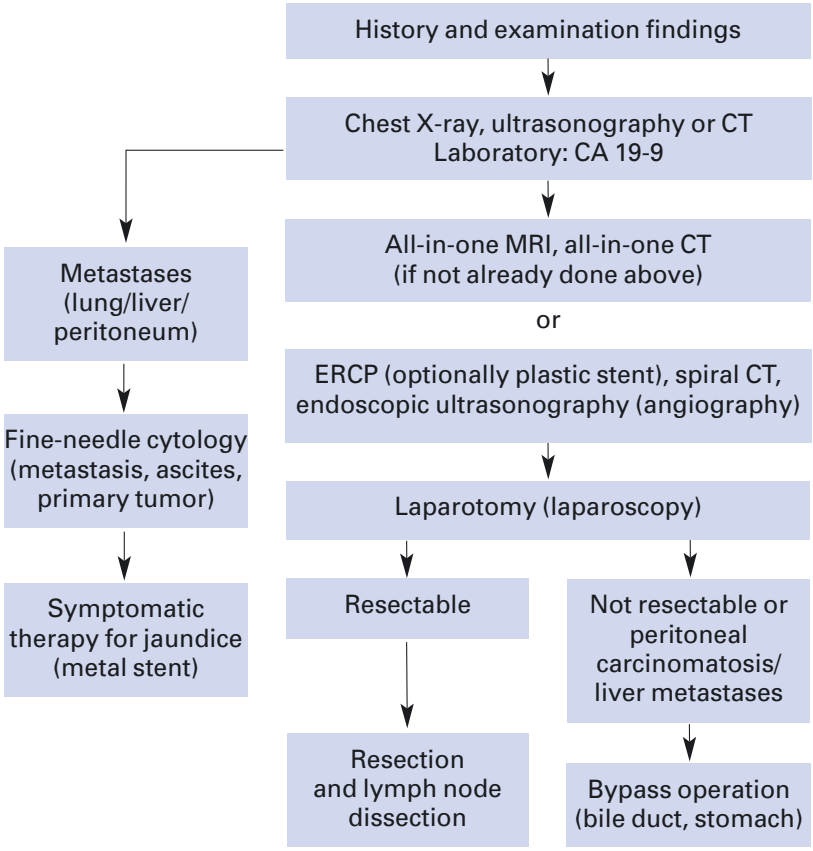
In centers with appropriate operative experience, pancreatic surgery may be offered with a high degree of safety (low morbidity and mortality). Quality assurance data show that the morbidity should be less than 40% and mortality less than 5%. In centers of defined excellence with pancreatic pathology, the resection rate is now 50% or greater for pancreatic carcinoma. The remaining patients can be referred for palliative therapy.

Patients with distant metastases (peritoneum, liver, lung) do not benefit from surgical measures. If jaundice is present, these patients are best managed with a bile duct endoprosthesis inserted endoscopically (metal stent). In rare cases, if this is not successful endoscopically, the bile duct may be stented transhepatically using PTCD.

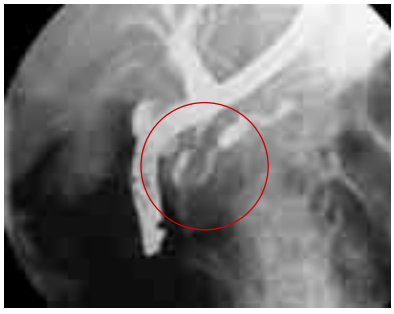
All remaining patients who do not have obvious metastases should be at least considered for operative measures, since there is at least a chance for curative therapy, or even long-term palliation if the neoplasm is clinically resectable (i.e. no gross unresectable disease).

The surgical treatment of carcinoma of the head of the pancreas involves a partial pancreaticoduodenectomy (Whipple operation). Generally, it is now possible to preserve the distal stom-

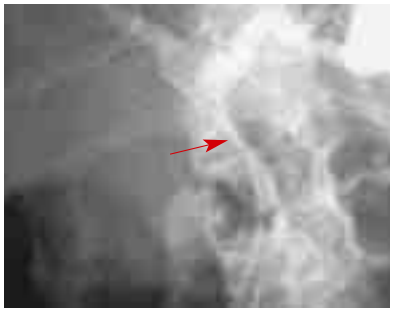
Diagnosis and Therapy in Patients with Suspected Carcinoma of the Pancreas



Stenting



ERCP with double duct sign (◯) in carcinoma of the head of the pancreas.



Plastic stent (arrow) in the bile duct for treatment of jaundice.

ach and pylorus in these patients (pylorus-preserving partial pancreaticoduodenectomy). The pancreas is transected at the neck of the gland overlying the portal vein, and the entire pancreatic parenchyma to the right of the portal vein is removed, along with the duodenum and distal extrahepatic bile ducts plus the gallbladder. Reconstruction is carried out by anastomosing the remaining left portion of the pancreas, the hepatic duct, and the stomach or postpyloric duodenum with a limb of jejunum. Radical resection of the head of the pancreas includes a form of oncologically orientated lymph node dissection.

In the case of locally inoperable cancer, jaundice is treated by a bilio-intestinal anastomosis, either a hepaticojejunostomy (combined with a cholecystectomy) or on occasion a choledochoduodenostomy. If there is duodenal compression with symptoms of gastric outflow obstruction, an operative bypass in the form of a gastroenterostomy (gastrojejunostomy) is undertaken; many surgeons perform a gastrojejunostomy routinely (even in patients without symptoms or for 'impending' duodenal obstruction) in an attempt to prevent later duodenal obstruction – a so-called 'prophylactic gastrojejunostomy'.

Carcinomas of the body and tail of the pancreas are generally unresectable at the time of presentation because of their late presentation. In exceptional cases, a left pancreas resection with splenectomy (distal pancreatectomy) and lymph node dissection may be appropriate; rates of cure when the lesion is 'resectable' are similar to those for cancer of the head of the pancreas. In addition, because pancreatic cancer is often (>50%) complicated by severe epigastric and back pain, many surgeons also perform a celiac plexus block (chemical splanchnicectomy) by injecting a neurolytic agent into the nerves in the celiac plexus in an attempt to prevent the development of pain in the future.

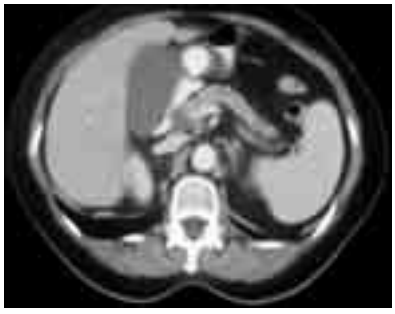
Chemotherapy and Radiotherapy

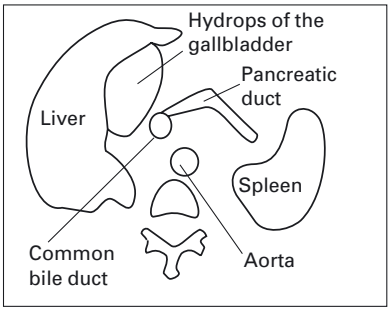
To date, conventional chemotherapy and radiotherapy of pancreatic carcinoma have not been convincing due to disappointing results and low rates of significant response. The use of 'adjuvant' chemotherapy and radiotherapy after a 'curative' pancreatectomy is controversial. Encouraging clinical data have been provided, particularly from Japan, with 5-year curative rates of up to 30% after radical operative treatment combined with adjuvant chemotherapy and radiotherapy. These data are currently being studied in controlled clinical trials in Europe and the United States. The results of the first European study on adjuvant treatment are available (ESPAC-1). In this trial with four study arms (observation, chemotherapy/radiotherapy, chemotherapy alone and both combined), there was a significant survival benefit only of adjuvant chemotherapy after pancreatic resections (median survival 19.7 months compared with 14 months without treatment). Radiation therapy did nor appear to add any benefit. Chemotherapy regimens applied regionally via the celiac trunk are also currently being evaluated in clinical studies as either adjuvant or neoadjuvant regional chemotherapy, in the latter case for downstaging of the tumor and subsequent resection. Time will tell whether using these multimodal therapeutic strategies will improve the discouraging prognosis of pancreatic carcinoma.

Complications

Obstructive jaundice
Gastric outlet obstruction
Acute pancreatitis (5% as the first sign of carcinoma)
Upper gastrointestinal hemorrhage (rare)
Ascites (advanced disease)
Splenomegaly/esophageal varices
Diabetes mellitus
Steatorrhea
Thrombophlebitis migrans
Thromboembolic disease

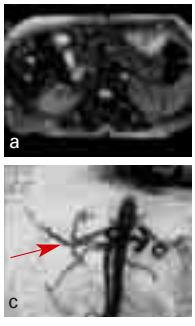
CT Diagnosis



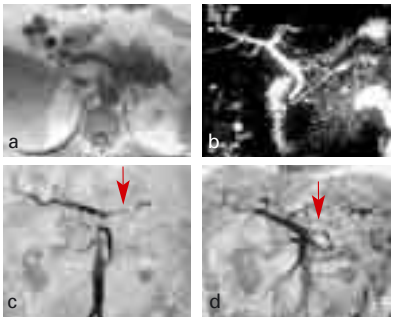


Dilatation of the pancreatic and bile duct as a result of carcinoma of the head of the pancreas (double duct sign).

MRI and MRCP



Pancreatic carcinoma (a) with obstructive jaundice (b): double duct sign on MRCP. Left hepatic artery (arrow) from the superior mesenteric artery (c) and partial occlusion (arrow) of the superior mesenteric vein (d).



Advanced carcinoma of the tail of the pancreas (a) with duct occlusion in the tail region (b). Infiltration of the splenic artery (c) and occlusion of the splenic vein (d).

Hormone and Antibody Therapy

In addition to palliative drug treatment, various hormone therapies were tried in the past, e.g. with tamoxifen or LH-RH analogues, because it was shown that sex hormone receptors are expressed in pancreatic carcinoma tissue. With this approach of antihormonal therapy, unfortunately, no clinical benefit could be demonstrated. One possible reason for this negative result may be that pancreatic carcinomas express these sex hormone receptors to a varying extent. Since the expression of somatostatin receptors was also found to be increased in pancreatic carcinomas, the efficacy of the somatostatin analogue octreotide at high dosage (6 mg/day) was also evaluated but with a negative result. Postoperative adjuvant therapy with monoclonal antibodies to pancreatic carcinoma cells after 'curative' resection also did not offer any advantages in survival. Hope is being placed in new generations of more specific antibodies that do not themselves induce antibody formation against the antibodies used for treatment (e.g. chimeric antibodies) and in other immunomodulators (interferon, interleukin α, etc.).

Operative Therapy

Contraindications
Distant metastases (liver, lung) Major vascular involvement (superior mesenteric artery) Comorbidity of the patient

Operative Procedures

Explorative laparotomy (after preoperative staging) with or without staging laparoscopy
Partial pancreaticoduodenectomy (classic Whipple)
+ radical lymph node dissection
Pylorus-preserving partial pancreaticoduodenectomy
+ radical lymph node dissection
Resection of the left portion of pancreas with splenectomy (distal pancreatectomy)
+ radical lymph node dissection
Palliative measures: hepaticojejunostomy or choledochoduodenostomy, gastrojejunostomy, celiac plexus block

Advantages of Pylorus-Preserving Whipple

Organ-preserving procedures (stomach)
Reduced operation time
Lower blood loss
Better gastrointestinal function
Better quality of life

Postoperative Complications after Whipple Procedure

	%
Morbidity	25–40
Anastomotic ulcer	5–10
Delayed gastric emptying	10–30
Mortality	should be < 5

Prognosis

The 5-year survival of pancreatic carcinoma ranges from 1% to a maximum of 10% worldwide. Thus pancreatic cancer is among the malignancies with the worst prognosis. Eighty percent of patients already have metastases at the time of diagnosis, and 60% of all resectable pancreatic carcinomas have lymph node metastases in the pathologic specimen after curative resection. Untreated pancreatic carcinoma leads to death within 1–2 months. Palliative treatment eventuates in death within 3–6 months, and even after 'curative' resection, mean survival is only 9–18 months. Overall 5-year survival after curative resection varies from 8 to 23%, depending on the series reported and selection criteria for resection. In view of the increase in the incidence of this terrible malignancy, our efforts in the future must be directed at making an early diagnosis and improving the results of treatment through combined treatment modalities (e.g. surgery + radiotherapy + chemotherapy + immunotherapy/immunomodulation).

Prognosis

	Average survival
Untreated	1–2 months
Palliative therapy	3–6 months
Operative therapy	9–18 months
5-year survival after curative resection	8–23%

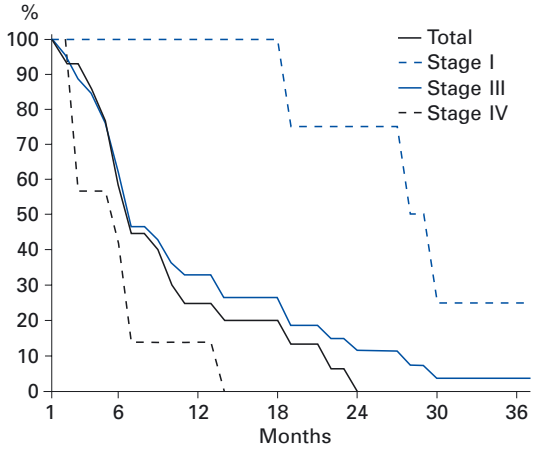
Adjuvant Therapy

Neoadjuvant Therapy

Treatment modality	Median survival months	2-year survival %
FAM	23	27
5-FU/FA	20	–
EBRT 40 Gy/5-FU	13–20	38–46
EBRT 50 Gy/Gem	16	39
Regional chemotherapy	23	–
EBRT/5-FU/Mit	16	43
EBRT/5-FU/Pac/Gem	21	–

FAM = 5-FU, Adriamycin, mitomycin C. 5-FU = 5-Fluorouracil. FA = Folic acid. EBRT = Percutaneous radiotherapy. Mit = Mitomycin. Pac = Paclitaxel. Gem = Gemcitabine.

Prognosis after Surgery



Statistical survival after surgical treatment depending on the stage of neoplasm.

Periampullary Carcinoma

In contrast to pancreatic carcinoma, periampullary neoplasms have a better prognosis, with 5-year survivals after resection of 30–40%. It is therefore important for patient and doctor alike to differentiate pancreatic carcinomas from periampullary tumors.

Classification of Periampullary Neoplasms

Three distinct forms of periampullary neoplasms should be distinguished: carcinomas of the distal bile duct, ampullary carcinomas (carcinoma of the ampulla), and duodenal carcinomas. Like pancreatic carcinomas, periampullary neoplasms are also classified according to the TNM system.

Pathologic Anatomy

These neoplasms differ from pancreatic carcinoma with regard to growth kinetics and metastatic behaviour, which explains their better prognosis. While with pancreatic carcinoma the resectability is 20% at the time of diagnosis because of the advanced stage, with periampullary carcinoma, the situation is quite the opposite with a resectability of 80%, and only approximately 30% of resected periampullary neoplasms have lymph node metastases. As with colonic carcinoma, an adenoma-carcinoma sequence has been well described for neoplasms of the papilla.

Clinical Picture

Because of the location of this neoplasm close to or involving the ampulla of Vater, the clinical picture is similar in many respects to that of carcinoma of the head of the pancreas. Patients with distal bile duct and ampullary carcinomas present with symptoms early in their course because of early obstruction of the distal bile duct leading to jaundice. In contrast, patients with duodenal carcinomas generally present with obstruction of the duodenum or upper gastrointestinal hemorrhage.

Diagnosis

The diagnosis begins, as with exocrine pancreatic carcinoma, with an initial CT or ultrasonography. If a periampullary neoplasm is suspected, an upper gastrointestinal endoscopy may be helpful in obtaining an objective diagnosis of carcinoma by biopsy. Distal bile duct carcinomas can be seen on ERCP, usually as an obstructed bile duct but without pancreatic ductal involvement; this finding should provide a strong clue that the patient does not have pancreatic (ductal) cancer. Prior to surgery, a contrast medium-enhanced CT or MRI is necessary for staging of the cancer. Further diagnostic measures are usually not necessary.

TNM Classification (UICC 1997)

T classification

- T_X primary neoplasm cannot be assessed
- T_0 no indication of primary neoplasm
- T_{is} carcinoma in situ
- T_1 neoplasm limited to the pancreas, ≤2 cm in its largest dimension
- T_2 neoplasm limited to the pancreas, >2 cm in its largest dimension
- T_3 neoplasm extends directly into the duodenum, common bile duct, and/or peripancreatic tissue
- T_4 neoplasm extends directly into the stomach, spleen, colon and/or neighboring large vessels

N classification

- N_X regional lymph nodes cannot be assessed
- N_0 no regional lymph node metastasis
- N_1 regional lymph node metastasis
  - N_{1a} Metastases in one single regional lymph node
  - N_{1b} metastasis is several regional lymph nodes

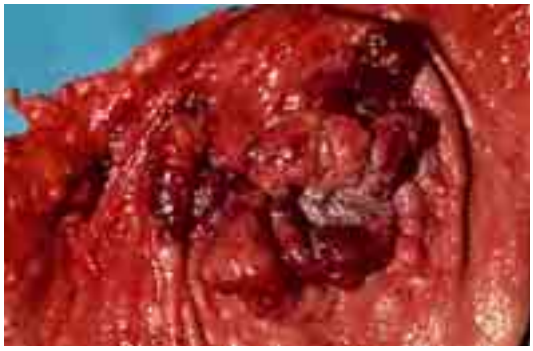
M classification

- M_X distant metastases cannot be assessed
- M_0 no distant metastases
- M_1 distant metastases

Periampullary Neoplasms

Papillary adenoma
(villous adenoma)
Ampullary carcinoma
Duodenal carcinoma
Distal bile duct carcinoma

Ampullary Carcinoma



Macroscopic preparation. 2-cm-large ampullary carcinoma.

Treatment

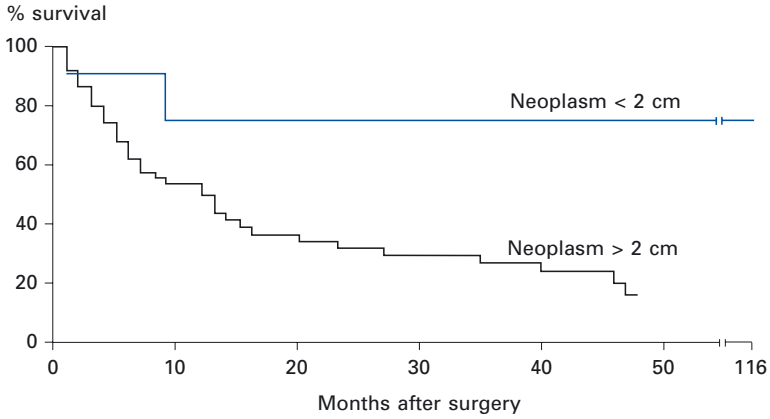
About 80% of all periampullary carcinomas can be resected surgically. Generally, a pylorus-preserving partial pancreaticoduodenectomy (pylorus-preserving Whipple operation) is performed. As with pancreatic carcinoma, a peripancreatic lymph node dissection is also suggested.

For the 20% of patients with nonresectable neoplasms, consideration is given to a surgical bypass (hepaticojejunostomy or choledochoduodenostomy) with a gastrojejunostomy to bypass the duodenum. If metastases precluding curative resection are evident preoperatively (liver, lung) and there are signs of obstructive jaundice, palliation may be best provided by endoscopic or transhepatic insertion of a bile duct prosthesis. For small ampullary carcinomas (up to 1 cm in size) or peri-Vaterian adenomas, an ampullectomy (removal of the ampulla with operative reinsertion of the common bile duct and pancreatic duct) may be performed, especially in patients with severe medical comorbidities.

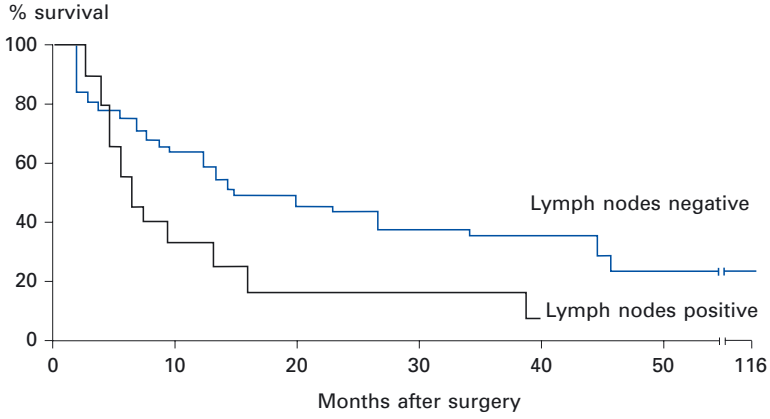
Prognosis

Compared with exocrine pancreatic carcinoma, periampullary neoplasms have a 5-year survival of 30%. The prognosis is therefore good from the oncologic viewpoint and, whenever possible, surgical resection using oncologic principles should be attempted.

Survival Rate Depending on the Size of Neoplasm



Survival Rate Depending on Lymph Node Involvement



Prognosis of Periampullary Carcinomas

Current 5-year survival rates after pancreaticoduodenectomy		
	Mean, %	Range, %
Ampulla of Vater	40	28–70
Distal common bile duct	22	17–33
Duodenum	25	33–68

Endocrine Pancreatic Neoplasms

Endocrine pancreatic neoplasms are classified as benign or malignant neoplasms of the neuroendocrine system of the pancreas, i.e. so-called neuroendocrine or islet cell neoplasms. For the classification of these neuroendocrine tumors (NET), the functional classification has proved most useful according to the hormones that are clinically active in the neoplasm.

The two most frequent endocrine neoplasms of the pancreas are insulinoma (approximately 75% of patients) and gastrinoma (approximately 20% of patients). All other endocrine pancreatic neoplasms are extremely rare and are found in the literature, usually, as case reports.

Insulinoma

Approximately 75% of all endocrine pancreatic neoplasms present clinically as insulin-producing islet cell neoplasms. Over 90% of insulinomas are benign. A third of insulin-producing neoplasms arise in the body of the pancreas, a third in the head of the pancreas, and a third in the tail of the pancreas. Approximately 80% of insulinomas occur singly, with a mean tumor size of 1–3 cm.

Clinical Picture and Diagnosis

The symptoms of an insulinoma are generally characterized by neurologic signs caused by the hyperinsulinemic hypoglycemia. Very frequently, patients present with loss of consciousness, which may masquerade as a primary neurologic disease. It is not unusual for an insulinoma to be mistaken for epilepsy.

The diagnosis of insulinoma is made through a 72-hour fasting test. The patient has to fast for up to 72 h, with simultaneous and continuous recording of blood glucose, insulin and C-peptide levels. In the case of an insulin-producing pancreatic neuroendocrine neoplasm, during this test there is a fall in blood glucose concentration with a concomitant rise in insulin and/or C-peptide. This demonstrates the autonomous insulin secretion, which is independent of blood glucose concentration, and is virtually diagnostic of an insulin-producing neoplasm.

In an attempt to localize the site of the insulinoma, CT may be the most cost-efficient imaging test. However, the sensitivity of this investigation is only about 50%. Recently, endoscopic ultrasonography has also been used for diagnosing endocrine pancreatic neoplasms, with a much higher detection rate (80%) in experienced hands.

MRI of the abdomen may also be used before surgical therapy of insulinoma. Along with selective angiography of the celiac trunk, these investigations have the highest sensitivity in the detection of insulin-producing neoplasms (over 80%). Insulinomas of the pancreas often show excessive uptake of contrast medium (hypervascularization). If the insulinoma cannot be seen after all diagnostic imaging techniques have been exhausted, in the case of a clear-cut fasting test, surgical exploration should be performed, since 95% of endocrine pancreatic neoplasms are found intraoperatively, especially if the surgeon also utilizes intraoperative ultrasonography.

One special situation should be discussed, i.e. factitious hyperinsulinemia secondary to exogenous administration of insulin – usually by someone in the medical profession who has access to parenteral insulin. This clinical scenario mimicks that of an insulinoma with episodes of hypoglycemia in conjunction with an increased serum

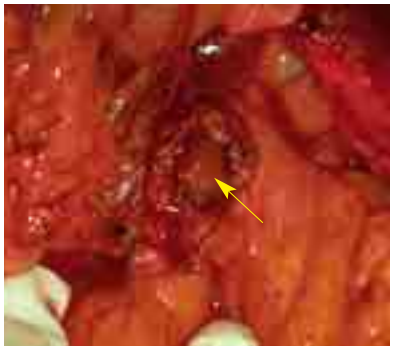
Classification

Type	Incidence %	Mutation rate, %	Hormone	Extrapancreatic location, %
Insulinoma	75	<10	insulin	1
Gastrinoma	15–20	>50	gastrin	20–40
Vipoma	1–2	>50	vasoactive intestinal polypeptide	5–20
Glucagonoma	1–2	>70	glucagon	rare
Somatostatinoma	<1	>50	somatostatin	frequent
PPoma	<1	?	pancreatic polypeptide	?
Carcinoid	?	?	serotonin	?
Corticotropinoma	<1	>99	melanocyte-stimulating corticotropin	?
Hyperparathyroidism	<1	>99	?	?
Neurotensinoma	?	?	neurotensin	?
Calcitoninoma	?	?	calcitonin	?
Nonfunctional neoplasms	<5	>50	–	?

Clinical Features

Insulinoma	Frequency, %
Neurologic symptoms (dizziness, absence attacks, apathy, coma)	92
Cardiovascular symptoms (episodic palpitations, precordial pain)	17
Gastrointestinal symptoms (hunger attacks, nausea, vomiting)	9

Site of Operation and Macroscopic Appearance



Intraoperative site in the case of an insulinoma in the tail of the pancreas (arrow).

Macroscopic appearance of an insulinoma.

insulin level. However, in this situation, the serum C-peptide level remains low (no C-peptide in insulin preparations) while with a true insulinoma, C-peptide levels are high.

Treatment

The treatment of insulinoma is operative. Either enucleation of the endocrine neoplasm or resection of the affected pancreatic segment should be attempted. Since insulinomas are multiple in up to 20% of patients, intraoperative ultrasonography of the pancreas should be undertaken to exclude multiple insulinomas, especially in patients with the multiple endocrine neoplasia (MEN) syndrome, and to then treat accordingly.

Prognosis

The prognosis is generally good, since over 90% of the insulinomas are benign, so that with surgical treatment, cure may be achieved. The rare islet cell carcinomas are treated surgically in accordance with oncologic criteria.

Gastrinoma (Zollinger-Ellison Syndrome)

Approximately 20% of all endocrine pancreatic neoplasms are gastrin-producing tumors. In contrast to insulinomas, these neoplasms have a higher rate of malignant change (over 50%). Gastrinomas are on average 1–2 cm in size and are predominantly found in the triangle formed by the head of the pancreas, first and third portion of the duodenum (pars 1–3) and the common bile duct (the so-called gastrinoma triangle).

Clinical Picture and Diagnosis

The clinical picture of a gastrinoma is characterized by symptoms of severe unresponsive peptic ulcer disease because of the excess gastrin secretion by the neoplasm. The suspicion should arise in recurrent peptic ulcer, duodenal and gastric ulcers found in an atypical site, and in the combination of symptoms of peptic ulcer and recurrent diarrhea. The diagnosis is made via a serum gastrin assay, especially after stimulation with secretin. In response to secretin administration, there is an excessive rise in gastrin in the serum, which confirms the diagnosis of 'gastrinoma'.

Determining the site of the gastrinoma preoperatively is difficult but should always be attempted clinically. In the past, a contrast medium-enhanced CT of the abdomen and selective angiography of the celiac trunk and mesenteric circulation were used as the first diagnostic imaging modality. As in the case of insulinoma, gastrinomas are often hypervascular. Careful endoscopy of the duodenum with careful inspection and endoscopic ultrasonography have become the imaging procedure of choice of the mucosa. Recently, octreotide scintigraphy has been shown to be a very sensitive procedure in establishing the localization of NET, since these neoplasms have somatostain receptors. In addition, gastrinomas can often be detected by magnetic resonance imaging.

Diagnosis and Treatment of Insulinoma

History and examination findings

↓

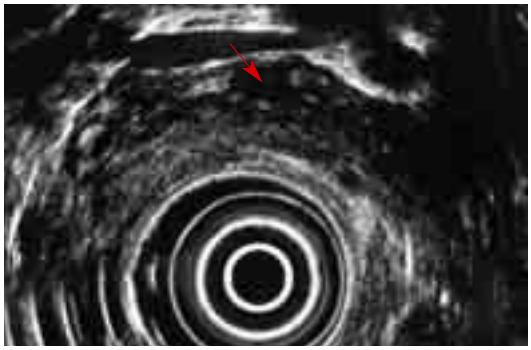
Fasting test

↓

Localization using endoscopic ultrasonography CT/MRI Angiography

↓

Surgery with intraoperative ultrasonography Enucleation Resection



Endoscopic ultrasonography. 7 × 5 mm echo-poor space-occupying lesion (arrow) at the junction of the head and body of the pancreas.

Provocation Tests

	Test	Clinical response
Gastrinoma	secretin test	rise in gastrin of over 100%
Somatostatinoma	calcium/ pentagastrin test	rise in somatostatin
Carcinoid	calcium/ pentagastrin test	flushing after 3 min, lasts for over 30 min
Insulinoma	fasting test	hypoglycemia, rise in insulin and C-peptide
Glucagonoma	no specific test	

Treatment

If a gastrinoma is found, surgical treatment should involve extirpation/resection of the tumor. Frequently (30–50% of the time), localization of gastrin-producing tumors is not successful; nevertheless almost all these neoplasms should be treated initially by an explorative laparotomy unless objective evidence of distant metastases is present. Careful intraoperative palpation, inspection and intraoperative ultrasonography enable the gastrinoma to be found and resected; many are found in the wall of the duodenum. Because of the high rate of malignancy (over 50%), a gastrinoma is, however, not infrequently encountered when it has already metastasized. Here surgical measures aimed at reducing tumor size (debulking) are recommended if the secretion of gastrin and its peripheral effects cannot be suppressed with high-dose, proton pump inhibitors.

Operative therapy of gastrinoma involves enucleation of the neoplasm, including if necessary a partial resection of the duodenum, or resection of the affected portion of the pancreas (e.g. partial pancreaticoduodenectomy).

When the primary neoplasm cannot be found at operation or in the palliative situation, consideration should be given to life-long administration of high-dose proton pump inhibitors, such as omeprazole, to reduce acid secretion, and somatostatin or its analogue octreotide for symptomatic therapy. Currently, there is almost no need to perform the previously common total gastrectomy for elimination of the target organ.

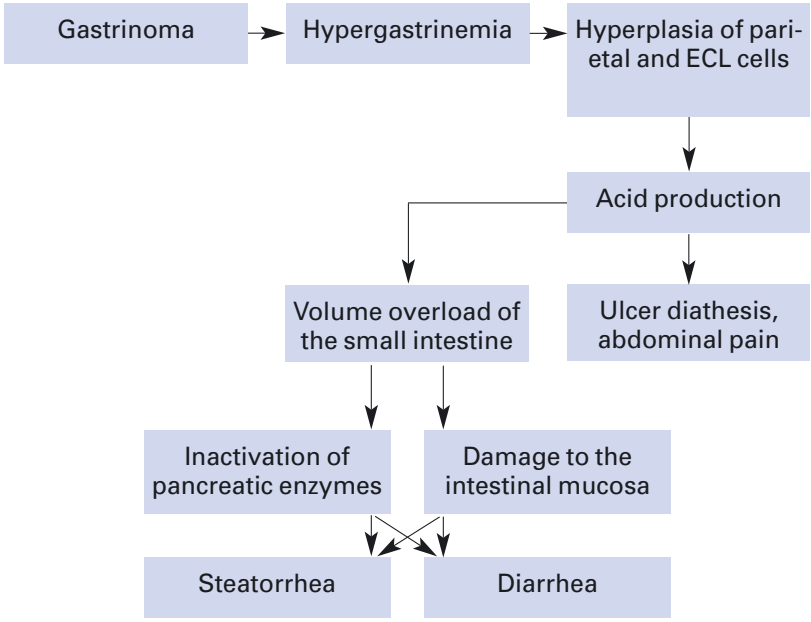
Rare Pancreatic Endocrine Neoplasms

In addition to the insulinoma and gastrinoma, in very rare cases there may be a vipoma, glucagonoma, pancreatic polypeptidoma or a carcinoid endocrine neoplasm of the pancreas; these neoplams are malignant in up to 90% of patients, and together account for at most 10% of all endocrine neoplasms of the pancreas.

The clinical signs and symptoms are either determined through the hormone produced by the neoplasm (vipoma: watery diarrhea; carcinoid: flushing; glucagonoma: hyperglycemia and characteristic skin symptoms). For diagnosis, an attempt should be made to identify the relevant excess hormone produced in serum. For determining the site of the neoplasm, the same procedure applies as for insulinomas and gastrinomas: endoscopic ultrasonography, contrast medium-enhanced CT/MRI, selective angiography of the celiac and mesenteric circulation, and octreotide scintigraphy.

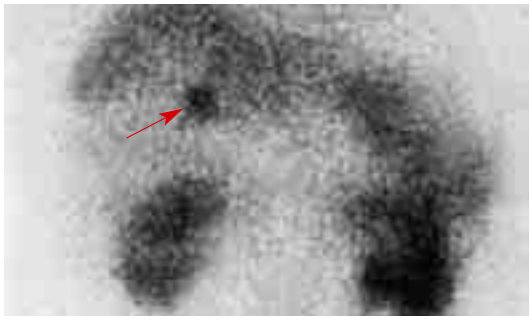
Another category of neuroendocrine neoplasms of the pancreas includes the so-called nonfunctional neuroendocrine neoplasms. These neoplasms also arise from islet or neuroendocrine cells, but they do not produce enough of a peptide hormone to cause a clinical syndrome of peptide hormone excess. Interestingly, if one stains for peptide hormones in the neoplastic tissue, one or more may be prominent; however, these hormones are either not released or not synthesized in large enough quantities to cause symptoms.

Pathophysiology of Gastrinoma



Octreotide Therapy for Inoperable NET

	Patients	Improvement of symptoms, %
Carcinoid	38	60
Vipoma	13	85
Glucagonoma	7	85
Gastrinoma	12	58
Insulinoma	12	41



Octreotide scan. Gastrinoma (arrow) projecting into the hepatoduodenal ligament.

Nonfunctional NET comprise 20–50% of all pancreatic neuroendocrine neoplasms. About half of these neoplasms behave malignantly.

In terms of treatment, surgical resection or on occasion debulking should be considered. Patients with advanced endocrine neoplasms of the pancreas may benefit from tumor debulking, since the leading symptom is usually hormone overproduction, which can be relieved or ameliorated by debulking.

In the advanced stage, palliative long-term therapy with the somatostatin analogue octreotide (administered subcutaneously) may be considered. In some circumstances, clinical control of the neoplasm over several years may be achieved by this method.

Prognosis

The prognosis of malignant NET of the pancreas varies greatly from individual to individual. In contrast to exocrine pancreatic carcinomas, patients with metastatic NET can have a good quality of life for several years, so that an individual assessment should be undertaken at the appropriate time interval depending on the stage.

Appendix

Pancreatic Surgery

As recently as the 1970s, pancreatic surgery was a very dangerous affair. The reasons for this were the lack of extensive experience with formal pancreatic resections, lack of earlier diagnosis of malignant diseases of the pancreas secondary to inadequate imaging modalities, and overall technical difficulties with the anatomy of the pancreas and the difficulty of anastomosing the pancreatic parenchyma to the bowel.

As a result of modern suturing and reconstruction techniques, but also because of advances in preoperative preparation and the postoperative care of the patient, pancreatic surgery should today be classified as a well standardized, relatively safe form of surgery in experienced centers. Specifically, this means that the mortality after operative therapy of necrotizing pancreatitis should be less than 20% in experienced hands. In surgery for chronic pancreatitis, mortality should be 1–2%. Neoplasms of the pancreas and periampullary carcinomas should now be resected with a mortality of less than 5%.

Surgical Procedures in Necrotizing Pancreatitis

Inflammation of the pancreas occurs in the retroperitoneum and not primarily intraperitoneally, that is, in the abdominal cavity.

The accepted method of choice for infected necrotizing pancreatitis involves the primary principle of necrosectomy combined with some form of drainage of the pancreatic bed and any involved areas of the retroperitoneum.

Drainage of the pancreatic bed may involve a closed lavage with continuous infusion/aspiration of a fluid which serves to 'debride' the area of necrosectomy. Alternatives to closed lavage include on the one hand 'planned re-laparotomy' or 'staged lavage', and on the other 'open packing' (open abdomen). In both procedures, instead of closed lavage, open lavage of the cavities of necrosis is performed with daily or every-other-day operative reexposure. Because of the frequent reoperations with surgical manipulation, there is a danger of complications (small intestinal fistulae, hemorrhage), so that the closed procedure is preferred by some groups. However, in experienced hands, the open procedures achieve just as good results compared with the closed-treatment approach.

Necrosectomy and Continuous Closed Lavage of the Retroperitoneum

The approach is via a median or transverse upper abdominal laparotomy. Access to the pancreas is achieved through the gastrocolic ligament between the stomach and transverse colon. The capsule of the pancreas is opened, and the peripancreatic areas of necrosis are carefully removed digitally and by blunt instruments. Only the well-demarcated areas of necrosis should be removed. Fresh adherent necrosis should be left in place because severe bleeding may occur if one attempts to sharply dissect the area of necrosis from the viable tissue to which it is adherent. After debridement of the peripancreatic areas of necrosis, necrosectomy of the pancreatic necrosis begins. Extreme care should be taken to avoid severe hemorrhage from the splenic vessels or from the portal vein. Again, only the well-demarcated areas of necrosis are removed. After necrosectomy of the pancreas, the retroperitoneal necrosis should be unroofed and the necrosis removed. In some circumstances, the retroperitoneal necrosis

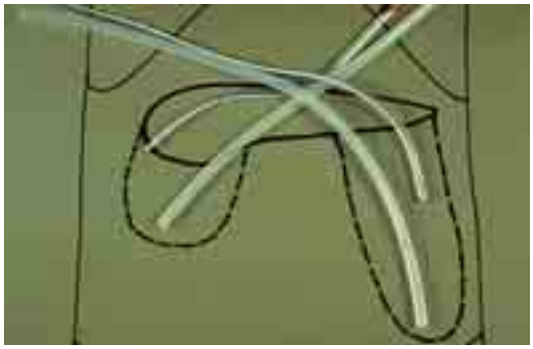
Surgical Procedures in Necrotizing Pancreatitis

Necrosectomy with closed lavage
Necrosectomy with staged lavage
Necrosectomy with open packing

Operation Site

Pancreas (arrow).

Lavage System for Closed Lavage Treatment



Bidirectional lavage catheter, schematically placed.

extends to the pelvis behind the ascending and descending colon. Following necrosectomy, a double-lumen lavage catheter is placed in the pancreatic bed as well as in the areas of retroperitoneal necrosectomy. The entry to the lesser sac is closed, so that there is a water-tight, peripancreatic/retroperitoneal lavage compartment. The lavage of the necrotic cavities begins intraoperatively with a weakly hyperosmolar lavage solution developed for continuous peritoneal dialysis (e.g. continuous ambulatory peritoneal dialysis solution). Within the first postoperative week, the lavage is conducted with quantities of 20–50 liters/day. A careful assessment of intake and output of the lavage solution every 2–6 h is important. After a week, and provided the patient has recovered from the septic clinical picture, the lavage quantity is reduced over 3-day intervals by 50% at each time. The lavage should not be stopped before the 3rd postoperative week, because pancreatic fistulae caused by the necrosectomy only begin to close from this time onwards.

Approximately one third of patients with necrotizing pancreatitis treated in this way require repeat surgery during the lavage treatment because of development of a late abscess of the pancreas, persistent, nonresolving fistulae or hemorrhage. With this approach, hospital mortality should be 10–20%.

Surgical Procedures in Chronic Pancreatitis

The surgical treatment of chronic pancreatitis is designed to treat the pain and the complications caused by the disease without prematurely precipitating the onset of diabetes mellitus by an extensive pancreatic resection. Thus, procedures such as an extended resection of the left portion of the pancreas (80–95% pancreatectomy), total pancreatectomy and, more recently, also partial pancreaticoduodenectomy now can often be avoided in this benign disease through use of a 'pancreas-preserving' technique.

Treatment Principle of Ductal Drainage

The principle of ductal drainage is considered in patients with a dilated pancreatic duct of over 8 mm diameter without additional complications of chronic pancreatitis. The principle of wide ductal drainage developed by Puestow and Partington-Rochelle results in 70–80% of patients being pain-free in the early postoperative period, with approximately 60% of patients remaining pain-free in the long term (5 years).

After exposure of the pancreas, the dilated pancreatic duct is opened over a distance of 4–15 cm by an incision through the pancreatic parenchyma. All calculi in the pancreatic duct should be removed. The pancreatic duct/parenchyma is then anastomosed to an isolated loop of the jejunum (Roux-en-Y principle). The surgical complication rate of this procedure is approximately 10–20%, and the clinical mortality is 1–3%.

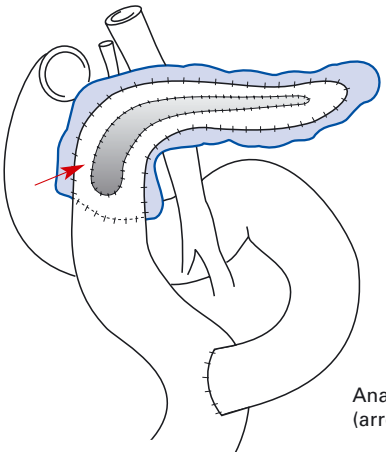
Treatment Principle of Pseudocyst Drainage

In pancreatic pseudocysts causing symptoms through a mass effect (≥6 cm), the principle of cystojejunostomy comes into play. It is important to exclude other complications of chronic pancreatitis, such as bile duct stenosis, a chronically inflamed, enlarged head of the pancreas, stenosis of the pancreatic duct, and vascular occlusion through a careful diagnostic work-up (ERCP, CT

Surgical Procedures in Chronic Pancreatitis

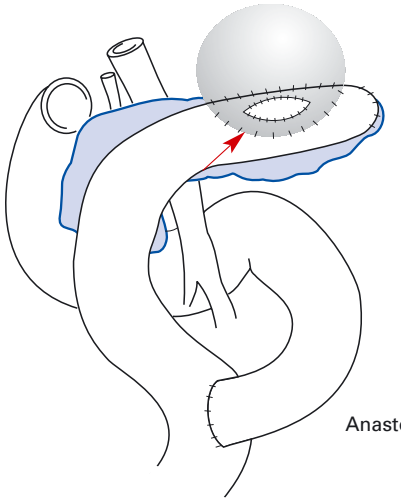
Drainage procedures	Resection procedures
Side-to-side pancreaticojejunostomy (Puestow/Partington-Rochelle procedure) Pseudocystojejunostomy	Duodenum-preserving resection of the head of pancreas Pylorus-preserving partial pancreaticoduodenectomy (Whipple) Distal pancreatectomy

Puestow/ Partington-Rochelle Operation



Anastomosis of the pancreatic duct (arrow).

Pseudocysto-jejunostomy



Anastomosis of pancreatic pseudocyst (arrow).

or MRI). One should also exclude a cystic neoplasm. If the pancreatic cyst is the only cause of symptoms, a cystojejunostomy is recommended; the cyst is opened, its contents removed, and a side-to-side anastomosis of 4–8 cm is undertaken with an isolated limb of jejunum. Using this procedure, operative mortality is also less than 3%.

Treatment Principles of Resection

One of the most important principles of surgery of chronic pancreatitis is avoidance of insulin-dependent diabetes mellitus. Thus, only small, circumscribed resection procedures are best considered. As late as the middle of the 1980s, partial pancreaticoduodenectomy (Whipple) or distal pancreatectomy were standard procedures in chronic pancreatitis. The situation is different today. Most pancreatic surgeons today believe that distal pancreatectomy, except in highly selected patients, should be avoided whenever possible in chronic pancreatitis, since the risk of causing diabetes is high whenever functioning pancreatic parenchyma is removed. If a distal pancreatectomy is necessary because of a lesion in the tail of the pancreas, the resection should be kept as small as possible (30% of the parenchyma). A spleen-preserving distal resection of the pancreas is recommended. The remnant pancreas should be anastomosed with an isolated limb of jejunum (pancreaticojejunostomy).

When operative treatment of chronic pancreatitis is necessary for chronic, incapacitating pain, resection of the head of the pancreas is usually necessary. The two procedures currently accepted include the pylorus-preserving partial pancreaticoduodenectomy and duodenum-preserving resection of the head of the pancreas.

In the pylorus-preserving partial pancreaticoduodenectomy, the entire head of the pancreas to the left of the portal vein and the duodenum, extrahepatic bile duct and gallbladder are removed. Reconstruction is done with a jejunal limb that is anastomosed with the remaining pancreatic remnant, the hepatic duct, and the postpyloric duodenum. The surgical complication rate of this procedure is fully 30–50%, and hospital mortality is less than 2% in experienced hands.

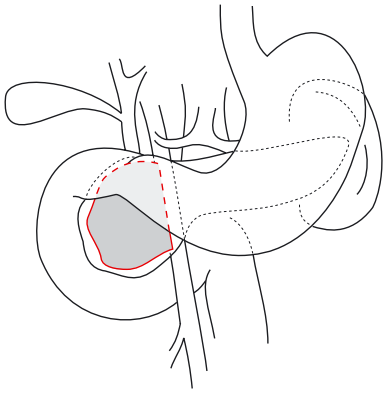
The other accepted principle in chronic pancreatitis with complications in the head of the pancreas (stenosis of the common bile duct, duodenal stenosis, inflammatory enlargement of the head of the pancreas, stenosis of the pancreatic duct, obstruction of the retropancreatic vessel stenosis) is a duodenum-preserving resection of the head of the pancreas. This procedure minimizes the risk of causing diabetes; after 5 years, 85% of patients remain pain-free, and two thirds of all patients can be reintegrated into a productive societal relationship.

The parenchyma within the head of the pancreas is subtotally resected in situ, while preserving enough vascular supply to maintain the viability of a narrow segment of parenchyma along the medial wall of the duodenum. As a result, the duodenum, bile duct, and retropancreatic vessels, as well as the pancreatic duct, can be decompressed. The reconstruction occurs through an isolated Roux-en-Y limb of jejunum. In the presence of simultaneous stenosis of the common bile duct or dilatation/stenosis of the pancreatic duct in the tail region, this operative procedure can be modified by opening the bile duct within the head of the pancreas and including this biliary opening into the jejunal anastomosis, filleting open the

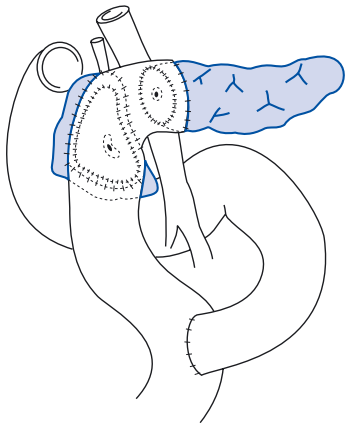
Surgical Indication for Duodenum-Preserving Resection of the Head of Pancreas

Tumor of the head of pancreas (chronic, inflammatory)
Treatment-refractory pain
Stenosis of the common bile duct
Stenosis of the pancreatic duct
Stenosis of the duodenum
Vascular complications (obstruction of portal, splenic and upper mesenteric veins)

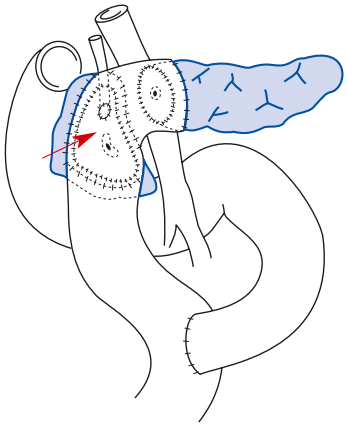
Duodenum-Preserving Resection of the Head of Pancreas



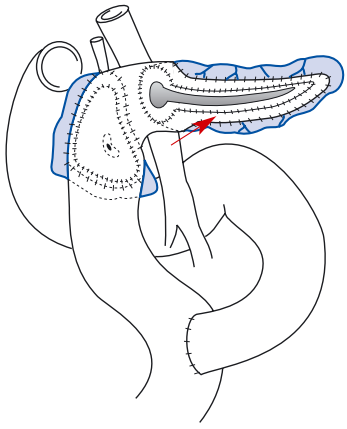
Extent of resection.



Reconstruction after duodenum-preserving resection of the head of pancreas.



Modification with additional inner bile duct anastomosis (arrow).



Modification with additional longitudinal pancreatic duct anastomosis (arrow).

pancreatic duct in the pancreatic remnant and including this opened duct also into the jejunal anastomosis. The procedure has a complication rate of 20% and a hospital mortality of <3%.

Surgery of Pancreatic Neoplasms (Malignancies)

The standard procedures for resection of carcinomas of the head of pancreas or periampullary carcinomas are partial pancreaticoduodenectomy (Whipple) and the pylorus-preserving partial pancreaticoduodenectomy. Whenever possible, the latter operative procedure is to be preferred.

The treatment principle is the radical removal of the neoplasm according to oncologic principles together with some form of lymph node dissection in the peripancreatic location. For proximal duodenal malignancies, a classic Whipple resection, which includes an antrectomy, should be undertaken. The operation requires a median or transverse upper abdominal laparotomy, mobilization of the head of the pancreas, cholecystectomy, resection of the entire pancreas to the right of the portal vein including the duodenum, extrahepatic bile ducts, and 30–50% of the stomach. Reconstruction is carried out with the upper jejunum as a pancreaticojejunostomy, hepaticojejunostomy, and an anastomosis with the stomach.

The postoperative complication rate of 30–50% is primarily related to the anastomosis with the pancreatic remnant. In periampullary carcinomas or carcinoma of the head of the pancreas, the remaining pancreas is frequently soft and difficult to anastomose. The hospital mortality in patients with pancreaticoduodenectomy should be less than 5% in experienced hands.

In neoplasms of the body and tail of the pancreas and in endocrine pancreatic neoplasms, a distal pancreatectomy may be necessary in 30–50% of patients. This procedure for malignancies or suspected malignancies is performed together with splenectomy, while in benign (endocrine) neoplasms, a spleen-preserving resection is preferred. The complication rate for resection of the left pancreas is 15–20%, while the hospital mortality is 1–5%.

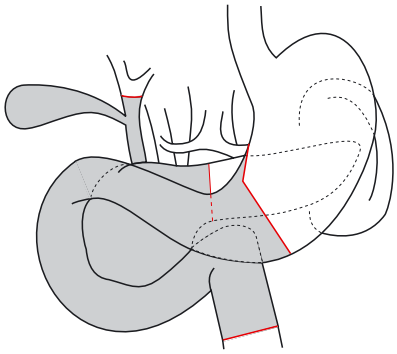
Endocrine neoplasms may also be enucleated locally, that is, the tumor is removed from the pancreatic parenchyma without a formal, anatomic pancreatectomy. Postoperative pancreatic fistula is a complication that can occur in about 10% of patients.

Despite thorough preoperative assessment and diagnosis, the final decision as to the appropriate operation is ultimately made intraoperatively. Contraindications to resection include the presence of distant metastases and/or involvement of the root of the mesentery. In these patients, a biliary-enteric bypass with or without a gastric bypass should be undertaken as a palliative surgical procedure.

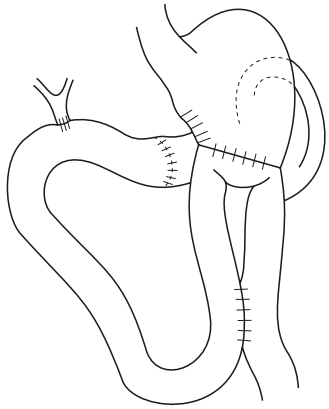
Operative Procedures in Pancreatic Neoplasms

Partial pancreaticoduodenectomy (classic Whipple)
Pylorus-preserving partial pancreaticoduodenectomy (PP-Whipple)
Resection of left pancreas with or without preservation of the spleen, depending on likelihood of malignancy
Enucleation (benign disease)
With malignancy, some form of lymphadenectomy

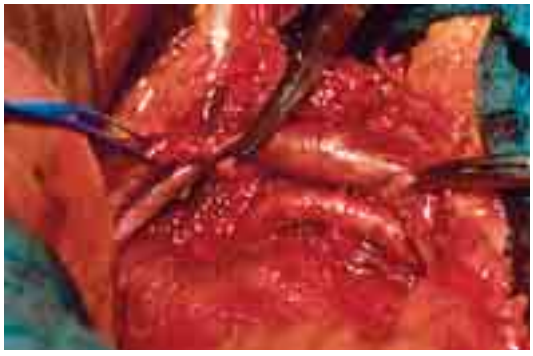
Classic Whipple Operation



Extent of resection.



Reconstruction in a classic Whipple operation.

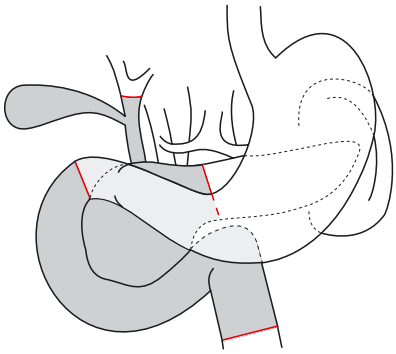


Intraoperative site after resection and extended lymphadenectomy; note the lack of lymphatic tissue in the mesenteric and aorto-caval vascular axis.

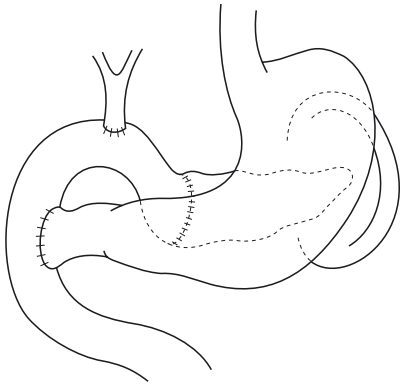
Perioperative Inhibition of Pancreatic Secretion in Elective Pancreatic Surgery

In the not too distant past, pancreatic surgery was feared, because resective procedures were associated with a high complication rate. The postoperative morbidity and mortality, which in the past were about 50% and 10%, respectively, are predominantly associated with management of the exocrine pancreatic secretions from the remnant gland after resection. Postoperative pancreatic complications include anastomotic leakage, pancreatic fistula, peripancreatic fluid or abscess formation, and septic multi-organ failure. Inhibitors of pancreatic exocrine secretion seemed to be attractive agents to evaluate in an attempt to minimize pancreatic exocrine-related complications after elective pancreatic surgery. The longer-acting somatostatin analogue octreotide was suitable for this purpose since this substance shows clear pharmacologic advantages over the native hormone (possibility for subcutaneous use, more potent action, longer half-life and now a very long-acting depot formulation that has a duration of action of up to 1 month). Four controlled, randomized clinical studies from Europe have demonstrated efficacy, so that perioperative administration of octreotide at a dosage of 3 × 100 mg daily is used in Europe as prophylaxis (like antibiotic prophylaxis in surgery to prevent wound infection). In contrast, 3 similar studies conducted in the United States exclusively in patients with pancreatic neoplasms have failed to show any benefit of perioperative, prophylactic octreotide, and thus, in North America, it is not used routinely. As a result of the development of modern tissue-sparing operative procedures, pancreatic surgery may today be offered to patients with pancreatic diseases with a high degree of safety (mortality <5%) and a low rate of complications (~30%).

Pylorus-Preserving Partial Pancreatico-duodenectomy



Extent of resection.



Reconstruction in pylorus-preserving Whipple.

Inhibition of Pancreatic Secretion with Octreotide

Author	Journal	Year	Patients	Complication rate, %		p
				placebo	octreotide	
European studies						
Büchler	Am J Surg	1992	246	55	32	<0.005
Pederzoli	Br J Surg	1994	252	29	16	<0.01
Friess	Br J Surg	1995	247	30	16	<0.007
Montorsi	Surgery	1995	218	36	21	<0.05
American studies						
Lowy	Ann Surg	1997	120	25	30	NS
Yeo	Ann Surg	2000	211	34	40	NS
Sarr	J Am Coll Surg	2003	275	42	40	NS

Reduction in postoperative complications in elective pancreatic surgery.

Congenital Diseases of the Pancreas and Pancreatic Abnormalities

Congenital Diseases of the Pancreas

These disorders include the most frequent of all inherited diseases in the Caucasian population, cystic fibrosis (mucoviscidosis), and other rare diseases, such as the Shwachman-Diamond syndrome and the Johanson-Blizzard syndrome. Isolated enzyme defects, involving lipase, colipase, enterokinase, trypsin, and amylase deficiency, are documented in the literature, but only as isolated case reports. In addition, there are several anatomic abnormalities, such as pancreas divisum, which may or may not present clinically or, as is frequently the case for annular pancreas, which usually becomes symptomatic in childhood.

Mucoviscidosis

Mucoviscidosis is the most frequent fatal inherited autosomal recessive disease and the most frequent cause of exocrine pancreatic failure and malabsorption in children and young adults. In the English-speaking world, it is termed cystic fibrosis (CF) because of its pathologic and anatomic changes. With modern techniques of molecular biology, the gene responsible for CF was cloned and characterized in 1989. This inherited disease is secondary to multiple possible gene mutations on the long arm of chromosome 7. In 70% of CF patients, there is a deletion of one of the base triplets in this gene (δF508), which leads to loss of phenylalanine in position 508 of a protein which transports chloride ions. The protein, also called CFTR (cystic fibrosis transmembrane conductance regulator), is localized in the apical membranes of epithelial cells. As a result of this genetic defect, all mucoprotein-secreting glands, but principally the pancreas and lungs, have disordered secretion. Over 300 mutations of this CF gene have now been described. The clinical manifestations (i.e. the phenotype) are, however, determined by the presence of the δF508 gene.

Epidemiology. The incidence of CF in the white population of Central Europe and North America is 1 per 2,000–3,000 live births. Five percent of the white population are heterozygous carriers of a mutated CF gene. CF is also found in other ethnic groups but more rarely. There is no difference in incidence between the two sexes. Since the successful cloning and sequencing of the CFTR gene, there has been a host of new data on the genetic diagnosis, pathophysiology, and possibility of gene therapy.

Pathophysiology. In normal apical epithelial cell membranes, the chloride channels open through phosphorylation mediated by ATP- and cAMP-dependent protein kinase. In CF, this is no longer possible because the CFTR gene defect leads to a characteristic impermeability of the epithelium for chloride ions. However, not all clinical manifestations can be explained solely by mutations in the CF gene. In CF epithelia, the outward rectifying chloride channels are also damaged. The protein responsible for this abnormality is not identical to the CFTR, but these two proteins do interact.

The primary consequence of the disordered mucoprotein secretion is a thick and highly viscous secretion with altered electrolyte composition and/or altered water content. In sweat and saliva of CF patients, there are higher sodium and chloride concentrations, and at least initially normal flow rates and volumes. This is an important

Cystic Fibrosis (Mucoviscidosis)

Autosomal recessive inherited disease	
CF gene defect on chromosome 7	(70 % δF508, > 300 mutations)
Incidence in the white population	1:2,000–3,000
Incidence in the black population	1:17,000
Male:female ratio	1:1

Complications

Meconium ileus	Cholestasis
Small intestinal atresia	Focal biliary cirrhosis
Rectal prolapse	Cholelithiasis
Distal intestinal obstruction	Steatorrhea
Episodes of acute pancreatitis	Diabetes mellitus

basis for the diagnosis of mucoviscidosis. In contrast, pancreatic secretion shows a reduction in sodium, chloride and bicarbonate content with an increased protein concentration. In the tracheobronchial and cervical secretions, the electrolytes are normal or reduced to a slight extent, but with a markedly reduced water content.

Histopathologically collections of eosinophilic secretions are found in the pancreatic ducts in association with intra- and interlobular fibrosis. In advanced stages, there is also acinar atrophy and liposclerosis as well as a reduction in the numbers of islets of Langerhans. In addition to the pancreas and apart from the lung – the most important organ affected – other gastrointestinal organs are also occasionally involved, such as the intestine, liver, and rarely the extrahepatic biliary system.

Clinical Features. The spectrum of the clinical picture of CF is wide and encompasses prenatal and neonatal disorders and other abnormalities that only occur during growth. Sometimes the disease is not detected until adult age, though this is uncommon. In newborns, a picture of intestinal obstruction dominates (meconium ileus). From very young childhood, chronic obstructive airways disease with recurrent infections (staphylococci and pseudomonas) is the hallmark of the disease and is predictive of the prognosis of CF patients. Pancreatic failure is seen in approximately 90% of patients, but may be well managed nowadays with the newer pancreatic enzyme preparations, such as Creon.

In a small percentage of patients, recurrent bouts of acute pancreatitis occur. Only approximately 5% of patients will eventually develop insulin-dependent diabetes mellitus.

Diagnosis. Using molecular biology methods (PCR), the responsible gene defect on chromosome 7 and other possible mutations may be identified with certainty in patients with CF. Such gene investigations are possible in peripheral blood cells and, in principle, all body cells. The method is time-consuming and expensive and thus cannot be performed as a prenatal and neonatal screening procedure, but is recommended in families with known members with CF.

In the neonatal period, the detection of increased albumin in the meconium is highly suggestive of CF; however, this test has very low sensitivity. A better screening parameter in this age group is assay of the serum trypsinogen, which is pathologically increased in neonates with CF and is an expression of the disturbed exocrine drainage/secretion.

If mucoviscidosis is suspected, a sweat test should be performed, analyzing the sodium and chloride content using pilocarpine iontophoresis. Reproducible chloride concentrations of >60 mmol/l in sweat are diagnostic of CF. Other diagnostic procedures include assay of fecal chymotrypsin or elastase 1 or an indirect pancreas function test, which has better sensitivity, such as the PLT or NBT-PABA test.

Treatment. In addition to a balanced diet assuring the calorie requirements of the growing child, adequate pancreatic enzyme replacement is important through oral administration of pancreatin preparations soluble in the small intestine (Creon®, Viocase®, or Pancrease® with lipase contents of at least 20,000 U). Colonic strictures have been reported in CF patients taking very concentrated capsular forms of enzymes. The di-

Diagnosis of Mucoviscidosis

	Notes
Identification of CF gene on chromosome 7	Specific identification, but 300 mutations are known This is not a cost-effective screening procedure
Sweat test	Highly sensitive initial test if CF is suspected
Serum trypsinogen	Sensitive in the neonatal period, suitable as a screening test
Albumin in meconium	Poor sensitivity as a screening test in neonates
Pancreolauryl test	Sensitive test to determine impairment of exocrine pancreatic function
Elastase 1/chymotrypsin in feces	Sensitive test to determine failure of exocrine pancreatic function

et should provide 120–150% of the recommended daily caloric requirements, with 15% proteins, 35% lipids and 50% carbohydrates. It is important that sufficient quantities of essential fatty acids are provided. A diet high in MCT may be useful for a short period of time. It is important to ensure that there is sufficient supply of trace elements as well as water-soluble and lipid-soluble vitamins.

Although controversial, gene therapy could become an important treatment option prolonging life in these patients. In animal experiments, normal CF genes were inserted using molecular techniques in respiratory and pancreatic epithelial cells with transient correction of the gene defect and proper expression of the CFTR protein; these experiments are proof of concept.

The prognosis of patients with CF is determined primarily by the pulmonary complications of the disease. The mean life expectancy has increased markedly in the last decade and is currently greater than 30 years as a result of aggressive pulmonary therapy, psychosocial management in specialist centers, and multiple support groups. Thus, in the future, this disease will become more important for specialists in internal medicine and gastroenterology.

Shwachman-Diamond and Johanson-Blizzard Syndrome

The Shwachman-Diamond syndrome and the Johanson-Blizzard syndrome are very rare inherited autosomal recessive diseases of the pancreas. The incidence of the Shwachman-Diamond syndrome is 1 case per 20,000 live births, with both sexes affected equally. The clinical symptoms include exocrine pancreatic failure, bone marrow depression, disturbance of bone formation, and small stature. Other clinical symptoms include impairment of lung function, hepatomegaly, tooth alterations, renal dysfunction, delayed puberty, and ichthyosis. The sweat test is normal. Most patients with this disease are diagnosed by two years of age, but occasionally the diagnosis is delayed until during puberty.

The main features of the Johanson-Blizzard syndrome, also an autosomal recessive disease without sex predilection, includes aplasia of the nasal wings, deafness, hypothyroidism, microencephaly, dwarfism, and the absence of permanent teeth in addition to exocrine pancreatic insufficiency. This disease may occur in families in whom CF is found.

Very rare families with hereditary pancreatic exocrine failure have been reported in combination with sideroblastic anemia and splenic atrophy, in association with aplasia or hypoplasia of the pancreas. Isolated defects of enzyme synthesis with the corresponding absence or deficiency of pancreatic secretion may occur as congenital conditions. Disorders of synthesis of lipase, colipase, amylase, trypsinogen and enterokinase have been reported.

The treatment of exocrine pancreatic failure as part of these congenital diseases involves adequate diet combined with adequate pancreatic enzyme replacement.

Shwachman-Diamond Syndrome

Main features	Possible association
Pancreatic insufficiency Bone marrow depression Metaphyseal dysostosis Small stature Sweat test normal	Pulmonary dysfunction Hepatomegaly Tooth abnormalities Renal dysfunction Delayed puberty Ichthyosis

Johanson-Blizzard Syndrome

Main features
Pancreatic insufficiency Aplasia of the nasal wings Hypothyroidism Microencephaly Absence of permanent teeth

Isolated Congenital Disorders of Enzyme Synthesis

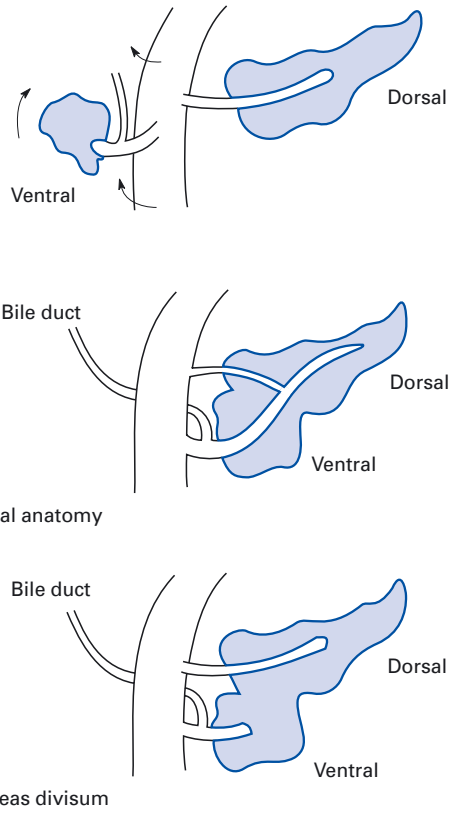
Lipase
Colipase
Amylase
Trypsinogen
Enterokinase

Abnormalities of the Pancreas

Annular Pancreas

This congenital abnormality is caused by abnormal migration of the ventral pancreatic bud during early gestation. The typical appearance is that of extrinsic compression of the 2nd portion of the duodenum. Annular pancreas usually presents in early childhood with duodenal compression (double bubble), but in about half the patients, it is clinically symptomatic only in adulthood. In adults, the symptoms are also due to duodenal obstruction with vomiting and epigastric pain. Jaundice occurs in a small number of patients. The incidence of acute or chronic obstructive pancreatitis is 15–40%.

Phase of Gestation

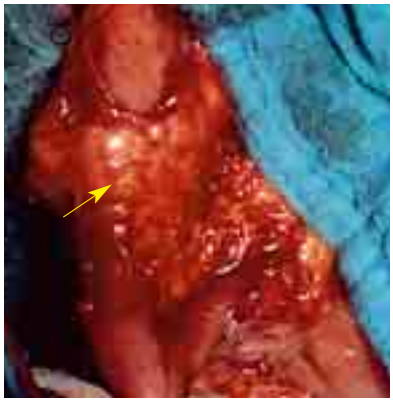


Embryology of the pancreas with rotation of the ventral portion and fusion (normal) or lack of fusion of the pancreatic ducts (pancreas divisum).

Pancreas divisum

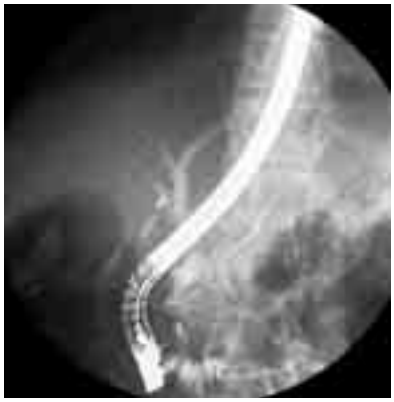
Pancreas divisum, the most frequent anatomic variant of the pancreatic ductal system, occurs when the pars ventralis and pars dorsalis fail to fuse with one another in the embryonic phase; this results in two separate outflow ducts. As a result, the dorsal portion of the pancreatic duct enters the duodenum via Santorini's duct and the minor duodenal papilla, while the short ventral portion of the pancreatic duct enters the duodenum via the major duodenal papilla. The common bile duct joins the ductal system of the ventral portion. There is also a rare, incomplete form of pancreas divisum in which the ventral portion communicates with the dorsal ductal system only via a small side branch, which on ERCP is only noted with increased injection pressures. Pancreas divisum has a frequency of 10% in the normal population and is only rarely a cause of disease. Its significance is discussed in the chapters on acute and chronic pancreatitis. If the minor duodenal papilla is too small, there can be a relative obstruction of drainage with stasis in Santorini's duct due to functional stenosis, with development of chronic obstructive pancreatitis. The treatment of choice for this condition is papillotomy of the minor duodenal papilla endoscopically or, if necessary, surgical sphincterotomy.

Annular Pancreas

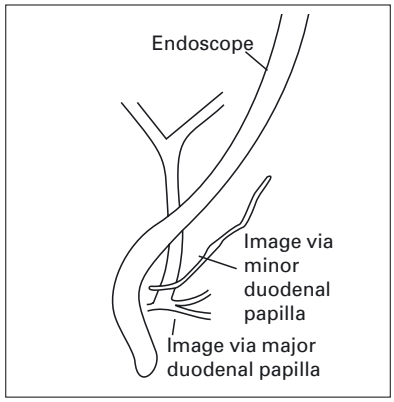


Intraoperative site. Duodenum encircled with pancreas tissue (arrow).

Pancreas divisum



ERCP view of pancreas divisum.



Main pancreatic duct opens at the minor duodenal papilla. The bile duct and ductal system of the ventral portion opens at the major duodenal papilla.

Pancreatic Trauma

Because of its retroperitoneal location, the pancreas is relatively well protected by the vertebral column, paraspinal muscles, and abdominal organs. Pancreatic injuries as a result of blunt or penetrating abdominal injuries are therefore rare, but when they do occur, they can be associated with severe complications. Pancreatic trauma occurs predominantly after blunt injury and is reported with a frequency of 3–4% of all patients with abdominal trauma. The typical scenario involves blunt injury to the abdomen via the steering wheel (e.g. head-on collision in a car, bicycle accidents in children). Approximately 90% of all patients with pancreatic trauma have one or more associated injuries. Pancreatic trauma is divided into 4 grades depending on the degree of the parenchymal damage.

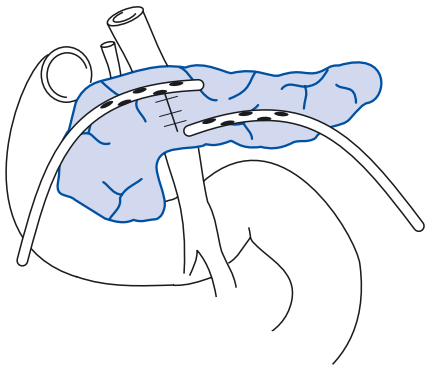
The mortality of pancreatic trauma is determined primarily by the associated injuries, but the mortality rate directly due to the pancreatic trauma is 6–10%, and morbidity is 20–40%. Pancreas-related complications include the following: pancreatic or duodenal fistula, pseudocysts, pancreatic abscess, posttraumatic pancreatitis (edema and even necrosis), hemorrhage, and sepsis (secondary to pancreatic abscess or infected pseudocysts).

In all penetrating injuries of the pancreas and in blunt abdominal trauma with hemorrhage, peritonitis, and raised serum pancreatic enzymes, there is a clear indication for surgical exploration of the pancreas. Severe pancreatic injuries overlooked as part of multiple trauma have a poor prognosis, thus the threshold for explorative laparotomy should be low. When the patient is stable but there is a suspicion of pancreatic injury, an ERCP should be undertaken in addition to CT to exclude possible disruption of Wirsung's duct. Definitive surgical treatment depends both on the associated injuries as well as the severity of the pancreatic injury. Grade 1 pancreatic lesions may be sutured in the early phase using monofilament suture, with wide peripancreatic drainage. If hematoma and necrosis are present, these should be debrided; in high-grade injuries (>grade 2) with ductal disruption, a resection may be necessary, especially with trauma of the body and tail of the gland. For pancreatic head trauma, extensive peripancreatic drainage is often preferred over resection because of the inordinately high morbidity and mortality of an emergency pancreaticoduodenectomy. The goal of drainage is to establish a controlled fistula. Administration of octreotide is recommended to decrease exocrine secretion.

The most common complication after trauma of the pancreas and/or surgery, along with pancreatic fistula, is abscess formation, which can be drained by radiologic interventional procedures. Late complications include stricture of the pancreatic duct with subsequent chronic obstructive pancreatitis.

Classification of Degree of Severity of Pancreatic Trauma

Grade 1	Hematoma, pancreatic contusion and/or rupture of the pancreatic capsule
Grade 2	Deep lesion of the pancreatic parenchyma with disruption of the pancreatic duct in the pancreatic body or tail
Grade 3	Deep lesion of the pancreatic parenchyma with disruption of the pancreatic duct in the head of the gland
Grade 4	Deep lesion of the pancreatic parenchyma with disruption of the pancreatic duct in the head with injury of the duodenum and/or bile duct



Grade 1 pancreatic injury. Suturing of the parenchyma and peripancreatic drainage.

Further Reading

Acute Pancreatitis

Randomized Controlled Studies

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