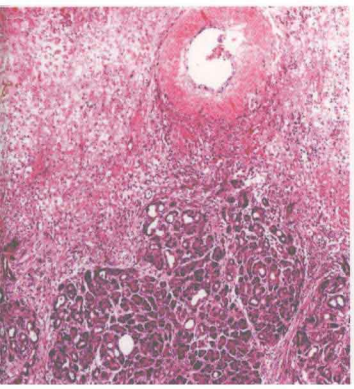
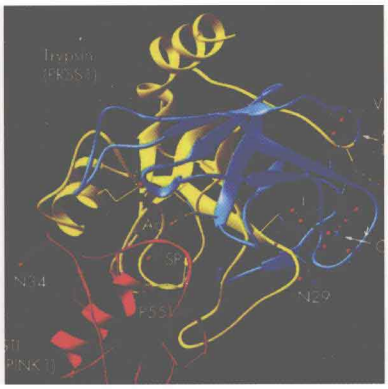
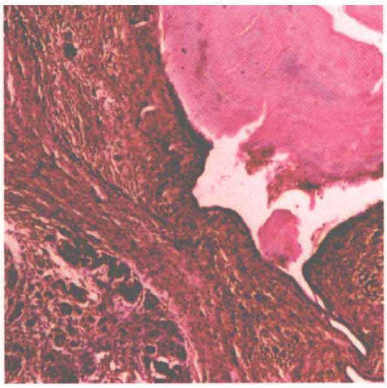
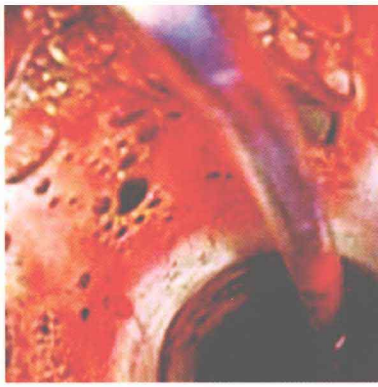
THE PANCREAS

AN INTEGRATED TEXTBOOK OF BASIC SCIENCE, MEDICINE, AND SURGERY

SECOND EDITION

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Preface

At the beginning of the 21st century, medicine is increasingly based on understanding the functions of genes and the molecular mechanisms of diseases. In pancreatology, the understanding of functions and dysfunctions of the exocrine and endocrine pancreas is derived from molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In clinical medicine new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal investigations. Decision making is increasingly based on the evidence of data from clinical trials on treatment modalities of pancreatic lesions.

Well into the 20th century the pancreas was considered a hidden organ. Now, at the beginning of the 21st century, only ductal pancreatic cancer remains largely an uncontrollable mystery disease. Today, understanding the pancreas, its normal and abnormal functions, and its morphological pathology has become an international focus of established scientists. Medical sciences are not uniform around the world. However, the impact of information technology, international data exchange, and global communications networks have resulted in a broadly increased level in the understanding and practice of pancreatology. The synergistic interaction of basic scientists, gastroenterologists, and gastrointestinal-tract surgeons in the field of investigative and clinical pancreatology has led to better understanding of pancreatic diseases through combining the knowledge of each to achieve the best evidence-based management. Although care of patients cannot be made a global affair, this book brings the most recent knowledge on the pancreas from international experts to readers everywhere.

The goal of this second edition of *The Pancreas – An Integrated Textbook of Basic Science, Medicine, and Surgery* is to provide the clinician with the most current data-based synthesis of understanding of pancreatic diseases, functional assessments, diagnostic and technical devices, and treatment options. A major part of this edition has been contributed by leading international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and diseases.

The editors acknowledge and are deeply indebted to all authors and co-authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to clinical decision making. Our profound gratitude goes also to all who were involved in the development and production of the book. We greatly appreciate their support.

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Contents

1 Definitions of pancreatic diseases and their complications

David C. Whitcomb and Hans G. Beger

Acute pancreatitis

Acute pancreatitis comprises different entities with regard to pathomorphology, clinical course, severity, and risks of disease: interstitial-edematous pancreatitis, necrotizing pancreatitis with infected or sterile necrosis, with or without intrapancreatic and extrapancreatic fatty tissue necrosis, pancreatic abscess, and pseudocystic lesion after pancreatitis [1].

Acute pancreatitis displays inflammation of pancreatic tissue secondary to acinar cell necroses. Apoptosis prevails in mild acute pancreatitis, necrosis in severe acute pancreatitis. In mild acute pancreatitis, the morphologic changes range from interstitial edema to minimal fat and exocrine tissue necrosis [2]. In severe acute pancreatitis, large confluent areas of pancreatic tissue necroses, frequently accompanied by hemorrhage into the tissue, are found. With the exception of infectious pancreatitis, which results from direct injury to the acinar cells by microorganisms and viruses, all other forms of acute pancreatitis are due to autodigestion by pancreatic enzymes independent of their etiology [2].

In terms of etiology, acute pancreatitis is frequently associated with gallstone disease or is the result of alcohol abuse but may also be caused by other factors such as shock, trauma, drugs, hypolipidemia, or hypercalcemia. Clinical signs of acute pancreatitis are sudden onset of upper abdominal pain, frequently with radiation into the back, accompanied by nausea, vomiting and distension of the upper abdomen. Biochemically, in about 80–90% of patients with acute pancreatitis, there is an increase in serum amylase and/or lipase concentrations at least three times the upper limit of normal serum levels. However, a subgroup of patients with acute pancreatitis do not have amylasemia and lipasemia despite onset of severe pancreatitis. The computed tomography (CT) criteria of acute pancreatitis are enlargement of the pancreas and edema accumulating in pancreatic tissues between acinar lobulations and necrotic areas, i.e., non-perfused tissue [3]. Frequently, retroperitoneal fatty tissue necrosis is present in addition to intrapancreatic necrosis [4].

Pancreatic necrosis

Pancreatic acinar cell necrosis and intrapancreatic fatty tissue necrosis are the typical lesions of acute pancreatitis. In mild pancreatitis disseminated, small, intrapancreatic and peripancreatic fat necrosis, with or without interstitial edema, is found. The key lesions of the pancreatic tissue are disseminated acinar cell, ductal cell and periductal tissue necroses [2]. Interstitial-edematous pancreatitis is accompanied by pancreatic and fatty tissue necrosis. According to the degree of tissue inflammation and the extent of the reduction in the microcirculation, necrotizing pancreatitis exhibits focal or diffuse necrosis or extended necrosis, which can be discriminated with contrast-enhanced CT [3]. Focal necrosis affects less than one-third to half of the pancreatic parenchyma, whereas extended necrosis includes more than 50% of the gland [5]. Dynamic contrast-enhanced CT is currently the gold standard for clinical diagnosis and location of pancreatic necrosis. Contrast density fails to exceed 50 Hounsfield units in areas of necrosis after intravenous contrast administration compared with well-perfused vital pancreatic tissue. Focal necrosis of the pancreas causes mild to moderate clinical symptoms. Mild pancreatitis resolves without complications with adequate clinical management. Extended necrosis mostly follows a severe clinical course, more than 50% of patients developing infection of necrosis [6]. The initial important complications in severe acute pancreatitis caused by extended necrosis are pulmonary insufficiency, with the need for mechanical ventilation, renal insufficiency, cardiocirculatory dysfunction, and shock [7]. The most important laboratory criterion for discriminating necrotizing from interstitial-edematous pancreatitis is C-reactive protein (CRP) concentration above 150 mg/L 48–72 hours after onset of the disease.

Pathophysiologically, necrotizing pancreatitis is a consequence of an autodigestive process that leads to tissue necroses of acinar cells and ductal epithelial tissue. In contrast, apoptosis (programmed cell death) is not dominantly observed in necrotizing pancreatitis during the period of acute inflammation. The predominance of apoptosis over necrosis has been associated with mild forms of pancreatitis; the opposite holds true for severe pancreatitis.

Infected necrosis

The key finding is colonization by intestinal bacteria of pancreatic parenchymal and intrapancreatic and/or peripancreatic fat necroses [8]. Hemorrhage in necrotic tissues may or may not be present. In most patients, infected necrosis is accompanied by systemic organ dysfunction, most frequently pulmonary, cardiocirculatory, or renal insufficiency. From a clinical point of view,

patients with pancreatic infections suffer a sepsis syndrome in addition to clinical and laboratory signs of acute pancreatitis. The diagnosis of infected necrosis is made by transcutaneous or ultrasound- or CT-guided needle aspiration of the necrosis and bacteriologic culturing of the aspirates [9]. A minority of patients have infected necrosis without sepsis. For this reason, a distinction has been made between contamination and infection of necrosis.

Pancreatic abscess

Pancreatic abscess is a circumscribed intraabdominal collection of pus, usually in proximity to the pancreas, that contains little or no pancreatic necrosis but which is surrounded by a pseudocapsulation. Pancreatic abscess does not develop before the fourth week after acute pancreatitis and is usually a late consequence of necrotizing pancreatitis after clinical acute pancreatitis [10]. The spectrum of bacteria found in pancreatic abscess is different from that found in primary infected necrosis, Gram-positive bacteria predominating over Gram-negative bacteria. Clinically, patients suffer the symptoms of an abdominal abscess. The content of the abscess consists of necrotic tissue and pus. The diagnosis "pancreatic abscess" has to be confirmed by bacteria-positive fine-needle puncture and/or contrast-enhanced CT.

Pseudocysts after acute pancreatitis

Pseudocysts are intrapancreatic or extrapancreatic fluid collections that are surrounded by a defined wall and which consist of connective tissue with inflammatory cells and adherent anatomic structures of neighboring organs. The fluid contains active enzymes and frequently necrotic tissue and inflammatory cells. In about one-third of patients, a connection to the pancreatic ductal system exists [1]. Development of pseudocysts after acute pancreatitis occurs late in the course. One-third of pseudocysts disappear spontaneously. Clinical symptoms are caused by compression of the splenic vein, stomach, large bowel, duodenum and surrounding structures.

Severe acute pancreatitis

Severe acute pancreatitis is identified by the development of local morphologic complications of acute pancreatitis and/or the occurrence of systemic organ dysfunction. Morphologically, patients suffering severe acute pancreatitis exhibit necrotizing pancreatitis, infected necrosis, sterile necrosis, pancreatic abscess, or a pseudocystic lesion after acute disease as well as retroperitoneal fatty tissue necrosis [11]. A high proportion of patients with necrotizing pancreatitis develop pulmonary insufficiency, renal dysfunction, cardiocirculatory depression or even shock, gastrointestinal bleeding, hematologic dysfunction, and liver insufficiency.

Early severe acute pancreatitis is present in patients who have, on admission to hospital, systemic organ complications such as functional pulmonary insufficiency, renal failure and cardiocirculatory depression in the 72 hours after onset [12]. These patients need maximum intensive care treatment; they have a high risk for systemic morbidity and a high risk of mortality. About 60% of the deaths following acute pancreatitis are caused by early severe acute pancreatitis in the first week of the disease [13]; 40% of deaths following acute pancreatitis with infected necrosis occur late in the course of the disease as a consequence of infected necrosis.

Pancreatic fistula

Three different types of pancreatic fistula are of clinical relevance: external postoperative fistula, internal pancreatic fistula, and pancreatic intestinal fistula caused by disruption of a pancreatic anastomosis.

An external postoperative pancreatic fistula is a communication between the pancreatic duct and the skin. An internal fistula is typically a communication between the pancreatic duct and intraabdominal organs or peritoneal or pleural cavities. An external postoperative pancreatic fistula is considered to complicate the postoperative course when, from the seventh postoperative day, more than 10 mL/day of an amylase-rich fluid can be evacuated [15]. A low-output fistula is defined as a fluid output below 200 mL/day and a high-output fistula as above 200 mL/day. A pancreatic intestinal fistula is a consequence of an anastomotic leak or disruption of the anastomosis with evacuation of intestinal contents [16]. This type of fistula is located between the small bowel loop used for pancreatic anastomosis and the skin, usually along the channel created by the drains or alongside the abdominal incisional wound [17]. Typically, an intestinal fistula is preceded by a peripancreatic abscess. Clinical symptoms are the same as for abdominal sepsis, with increasingly severe systemic complications [18].

An internationally accepted grading of external pancreatic fistulas has been established [19]:

- Grade A: transient fistula without clinical deterioration of the patient.
- Grade B: high-output pancreatic fistula frequently associated with clinical signs such as fever, leukocytosis, increase in CRP, and upper abdominal discomfort. It is recommended that the pancreatic anastomosis is checked using ultrasonography and CT in order to exclude a fluid collection or development of an abscess. Persistence of high-output fistulas beyond 2 weeks demands treatment, e.g. parenteral nutrition and administration of the somatostatin analog octreotide.
- Grade C: this is not a pancreatic fistula but an intestinal fistula after disruption of a pancreatic anastomosis. Patients develop clinical signs of abdominal sepsis. Urgent diagnosis and medical as well as interventional and surgical treatment are recommended [18,19].

Chronic pancreatitis

Definition of chronic pancreatitis

Chronic pancreatitis is a clinical syndrome defined by groups of signs and symptoms characteristic of longstanding inflammation of the pancreas. It is important to distinguish the general

definition of chronic pancreatitis as a syndrome from the clinical diagnosis of chronic pancreatitis because many of the signs and symptoms can occur as a result of conditions that do not include longstanding inflammation of the pancreas [20]. This distinction is relevant to clinical practice because a careless misdiagnosis of chronic pancreatitis can lead to inappropriate and potentially harmful interventions and treatments, stigmatization, and failure to address other condition.

The Marseille conferences in 1963, 1984, and 1988 defined chronic pancreatitis by morphologic, functional, and clinical criteria [21–23]. General morphologic features on histologic examination include irregular sclerosis with destruction and loss of exocrine parenchyma, dilation of ductal systems, inflammatory cells, and loss of acinar cells out of proportion to islet cells. It has been noted that all the histologic features may be seen regardless of etiology and that irreversible damage is present. The gross morphologic features of chronic pancreatitis were later subdivided into obstructive chronic pancreatitis, chronic calcifying pancreatitis, and chronic inflammatory pancreatitis. Functional features include the progressive and permanent loss of exocrine and endocrine function, although some functional improvement can be seen when an obstruction is removed. The clinical features include recurrent or persistent abdominal pain, although chronic pancreatitis is occasionally seen without pain. Other clinical features include evidence of functional loss of acinar cells with steatorrhea, and loss of islet cell function with diabetes mellitus.

The limitations of defining chronic pancreatitis as a syndrome have become apparent in cases where some, but not all, of the typical features are present or when an "early" diagnosis is desired. If the definition of chronic pancreatitis serves as the basis of diagnostic criteria, then what are the minimal and essential features? For example, experts vigorously disagree about whether a patient with abdominal pain but no clear morphologic features of chronic pancreatitis on abdominal imaging but with marginal reduction in bicarbonate concentration on a secretin-stimulation test has chronic pancreatitis or not. Accurately defining a group of essential features is also critical for developing and establishing model systems for experimental investigation.

The biological definition of chronic pancreatitis should be based on the abnormal presence of inflammatory cells within the pancreas (linked to the suffix "-itis") and on the qualifying term "chronic", which should be based on the type and function of active inflammatory cells within the pancreas rather than the clinical definition of time (e.g., duration >6 months). Based on this definition, the diagnosis of chronic pancreatitis would require evaluation of a representative tissue sample in which the nature of any active processes can be determined.

The characteristic histologic, functional, and clinical features of chronic pancreatitis should be a consequence of a chronic inflammatory process within the pancreas. In this case, the definition of chronic pancreatitis-associated complications follows naturally. However, it is often necessary to make a presumptive diagnosis based on standard signs and symptoms, and exclusion of other conditions that produce similar functional and clinical features.

Maldigestion in the chronic pancreatitis syndrome

Maldigestion refers to inadequate digestion of complex nutrients that are normally digested within the gastrointestinal tract. Maldigestion is distinguished from malabsorption, the inadequate uptake of normally digested nutrients from the gastrointestinal tract. Maldigestion in chronic pancreatitis occurs when the pancreas loses the ability to secrete sufficient quantities of digestive enzymes to digest the complex nutrients within the diet. When pancreatic enzyme secretion is below the amount needed to prevent maldigestion, the term "pancreatic insufficiency" is applied.

Maldigestion in chronic pancreatitis is usually clinically recognized only when the patient has advanced chronic pancreatitis, when most of the enzyme-secreting capacity has been lost and compensatory mechanisms have failed. The most common clinical sign is steatorrhea.

Maldigestion in chronic pancreatitis should be established by inclusion and exclusion criteria. Evidence of chronic pancreatic inflammation with destruction of acinar cells should be present, and either maldigestion or diminished pancreatic enzyme secretion must be evident. Conditions that should be excluded include malabsorption, maldigestion due to pancreatic enzyme destruction in the intestine (e.g., Zollinger–Ellison syndrome), or pancreatic insufficiency from other causes (e.g., Shwachman–Diamond syndrome, celiac disease, genetic deficiency of specific enzymes, blockage of the main pancreatic duct, major surgical resection). While the treatment of the latter disorders is similar to treatment of maldigestion in chronic pancreatitis, the etiology and other treatment considerations differ.

Low pancreatic juice bicarbonate concentration in the chronic pancreatitis syndrome

In humans, pancreatic juice contains concentrations of bicarbonate that may exceed 130 mmol/L. One of the functional consequences of chronic pancreatitis is a reduction in the amount of secretin-stimulated bicarbonate in pancreatic juice. The high bicarbonate concentration found in pancreatic juice originates from the duct cells, especially the more proximal duct cells where cystic fibrosis transmembrane conductance regulator (CFTR) expression is high. In patients with chronic pancreatitis and loss of normal parenchyma, the peak bicarbonate concentration is usually below 80 mmol/L. However, it has not been determined whether some *CFTR* mutations or defects in other ion transporters result in a diminished bicarbonate concentration without pancreatic inflammation. Thus, low bicarbonate concentrations are a sign of chronic pancreatitis, but it does not define chronic pancreatitis or exclude all other possibilities.

Fibrosis in the chronic pancreatitis syndrome

One of the most common complications of chronic pancreatitis is fibrosis. Fibrosis is the process of excessive deposition of fibrous matrix proteins in a tissue and is related to injury repair