Clinical Pancreatology
for Practising Gastroenterologists and Surgeons

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Clinical Pancreatology
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Foreword

Our knowledge in the field of pancreatology is continually accumulating. Relevant basic and clinical research studies, published in recent years, have provided new information that has changed our view of and approach to the diagnosis and therapy of pancreatic diseases. The challenge now is to disseminate these advances among all practicing gastroenterologists and surgeons treating pancreatic diseases, so that they will, in turn, benefit our patients.

This book, edited by Enrique Domínguez-Muñoz, is indeed a comprehensive treatise on clinical pancreatology. The carefully selected contributors are all dedicated pancreatologists of many years’ experience who have greatly contributed to where we stand today in the clinical management of pancreatic diseases.

The chapters on inflammatory and neoplastic diseases of the pancreas provide a complete and comprehensive insight into all clinical problems and offer solutions to everyday clinical needs in the management of pancreatic diseases. The individual aspects of diagnostic options, sometimes conflicting or even redundant, are presented in a very balanced and objective way. Clinical concepts are well illustrated and the reader can follow clear diagrams and excellent algorithms. The therapeutic sections, too, are very nicely developed and the necessary emphasis is given to the importance of an interdisciplinary approach. This is a particular requirement for all those who aim to operate successfully in this clinical field. The arguments put forward in several chapters go even beyond our state of the art knowledge and raise important considerations that will stimulate further clinical research.

Enrique Domínguez-Muñoz is to be congratulated for having thoughtfully selected topics corresponding to the sequence of decisions we need to consider when faced with the challenging problems of patients affected by an acute or chronic morbid condition of the pancreas. In my judgment this book is a must for specialists but also a gift to all clinicians who at times have to take responsibility for the care of patients with pancreatic pathologies.

Peter Malfertheiner
Preface

The pancreas continues to be, to some extent, the hidden organ for many gastroenterologists and surgeons. The diseases of the pancreas are frequently difficult to diagnose and/or treat, and the results of the treatment are usually disappointing. Mortality of acute pancreatitis remains high, diagnosis of chronic pancreatitis in its early stages is still a challenge, therapy of cystic fibrosis is far from satisfactory, and pancreatic cancer continues to be a devastating disease.

The exploration of the pancreas and its inherent difficulties has, over the last few decades, stimulated gastroenterologists, surgeons, radiologists, pathologists, and scientists to delve deep into their knowledge of molecular biology, genetics, physiology, pathophysiology, diagnosis, and therapeutic approaches to pancreatic diseases. Societies devoted to the study of the pancreas and its diseases have emerged all over the world and there is a demand for specific journals and books.

Many important advances have been made in pancreatology in recent years, many of them changing the approach to the patient with pancreatic diseases in clinical practice. Nevertheless, practicing gastroenterologists and surgeons, who face patients with pancreatic diseases daily, but who are not especially devoted to the field of pancreatology, can hardly apply these recent research advances to the management of their patients. In fact, pancreatology books and journals are highly specialized. Most of the knowledge contained therein has no direct clinical application and/or is difficult to comprehend for non-pancreatologists. Therefore, general gastroenterologists and surgeons have difficulty accessing the most recent and relevant advances in pancreatic diseases.

The goal of Clinical Pancreatology is to provide practicing gastroenterologists and surgeons with clear information regarding the current diagnostic and therapeutic approaches to pancreatic diseases. The book consists of short and concise chapters providing clear, evidence-based, but also experience-based, information, immediately relevant to clinical practice. Chapters have been written by internationally recognized gastroenterologists, surgeons, radiologists, and pathologists, specially dedicated to the study of the pancreas. This is, therefore, a book from expert pancreatologists for practicing medical doctors, in which controversies have been avoided as far as possible. Each chapter concludes with a list of the most relevant literature as “recommended reading” to provide readers with easy access to more detailed information.

As editor, I am deeply grateful and indebted to all authors for their dedication and efforts in contributing to this book. It is they who are really responsible for the high quality of this work. I also thank the team at Blackwell Science for their support, patience, and skill. Finally, my special thanks to Friederike Henniges, Global Medical Affairs Director of Solvay Pharmaceuticals, Germany, for her enthusiasm and support for this work.

J. Enrique Domínguez-Muñoz
I would like to dedicate this book to all the friends who have supported me throughout my professional life and who have helped me to grow, not only as a clinician but also as a person. Among all of them, I would especially like to thank Professor Peter Malfertheiner and Professor Fernando Carballo, who were, and still are, my teachers and friends.

The editing of this book has required dedication and a major effort. This has been possible thanks to the love, understanding, and support of my wife, Victoria, and my children, Irene and Enrique.

Finally, I would like to dedicate this book to my parents, Enrique and Concepción.
Overview

Acute pancreatitis is a protean disease, capable of resulting in pathologic findings ranging from mild pancreatic edema to total organ necrosis, and from regional retroperitoneal inflammation to systemic multiorgan failure. Depending upon the severity and scope of the underlying pathologic processes, acute pancreatitis may present anywhere on the spectrum of clinical severity, from mild abdominal discomfort to apocalyptic prostration.

Perhaps due to this very breadth in pathology and presentation, considerable clinical confusion has existed regarding acute pancreatitis. For much of the past century, standards did not exist to measure severity, nor were there any clinically useful definitions of acute pancreatitis and its complications. These deficiencies not only caused both researchers and clinicians to experience great difficulty in attempting to communicate with each other, but also resulted in idiosyncratic, and frequently conflicting, recommendations for therapy. As a case in point, during a personal 1980s literature search for articles restricted to “pancreatic abscess” a total of 45 reports were found, but only 11 had actually offered any definition of “pancreatic abscess,” the topic of their paper. Most troubling, however, was the observation that no two of these eleven definitions for “pancreatic abscess” were the same! Apparently, each of the authors had assumed that their working definition of “pancreatic abscess” was the same one used by everyone else, much as did Humpty Dumpty in Lewis Carroll’s Alice’s Adventures in Wonderland when he said, “When I use a word, it means just what I choose it to mean—neither more nor less!”

A further analysis of those disparate definitions of “pancreatic abscess” revealed that a variety of post-pancreatitic infections, such as infected fluid collections, infected pseudocysts, peripancreatic abscesses, and infected pancreatic necrosis, had been included under the single rubric of “pancreatic abscess.” This taxonomic confusion necessarily led to wide variations in proposals for diagnosis and therapy: proposed management for an infected pancreatic pseudocyst could hardly be expected to be successful if mistakenly applied to infected pancreatic necrosis. Clinical management for other complications of acute pancreatitis was similarly afflicted by confusing, and often conflicting, definitions.

Heterogeneous definitions of acute pancreatitis and its complications existed until relatively recently, being principally the result of the difficulty attendant upon attempting to study the natural history and variations of acute pancreatitis with the inadequate technology available at the time. Given the remote anatomic location of the pancreas, and the limitations of early noninvasive imaging, much of what was known (or thought to be known) about the pathology of acute pancreatitis was the result of autopsy or surgical studies. Clearly, material obtained from such studies could not be representative of those cases from the less severe spectrum of pathology. Inability to measure severity and the absence of precise disease definitions were therefore two of the major factors responsible for the prolonged delay in the development of a useful clinical approach to acute pancreatitis. From a historical standpoint, the first of these two problems to be addressed was the stratification of severity.
**PART I**

**Stratification of severity**

In 1974, John Ranson published his seminal paper on the stratification of severity of clinical acute pancreatitis. Using statistical manipulation of 43 clinical and laboratory variables obtained from a consecutive series of 100 patients with acute pancreatitis, he was able to identify 11 “prognostic signs” that proved to be significantly associated with clinical severity, as measured by the development of morbidity or mortality. For many subsequent years, these Ranson Criteria were all that were available to assign severity to an individual episode of acute pancreatitis. The necessity for severity assignment was nevertheless clear; in a disease process capable of wide variations in clinical severity, specific stratification of severity is necessary not only to compare the results of clinical investigations but also to predict patient prognosis. Today, we would add a third reason for determination of severity: selection among therapeutic options.

Despite the usefulness of the Ranson Criteria in comparing large patient populations, their ability to predict the severity of an episode of acute pancreatitis in individual patients was ultimately shown to be limited, being subject to error in as many as one patient out of every three. In addition to the recognized limitation in assigning severity to individual patients, the Criteria were also restricted by the often overlooked requirement that full assignment of severity was withheld until 48 hours following admission. Furthermore, it is equally important to point out that the Criteria have never been validated for any periods later than 48 hours. Even today, one can hear such incorrect statements as “there were four Ranson Criteria present at three days, five days.” Given these practical limitations in individual clinical application, and restriction to the initial 48 hours of the hospital course, it is not surprising that use of the Ranson Criteria has become decidedly less frequent today.

Over the succeeding years, a number of different approaches to the assignment of severity in an individual episode of acute pancreatitis have been proposed. These proposals have ranged from those based upon physical signs, to various predictive laboratory findings, to imaging features, to the results of clinical procedures, or to permutations and combinations of these approaches. An ideal system for assigning severity to an episode of acute pancreatitis would be consistently accurate, capable of being determined at any point in the episode, free of risk, simple and quick to perform, and inexpensive. To cut to the chase, at present no determinant of either the severity or the prognosis of an episode of acute pancreatitis has been identified that satisfies all of these optimal requirements.

The Acute Physiology and Chronic Health Evaluation (APACHE) II is perhaps the best system for stratifying the severity of an individual episode of acute pancreatitis available today. The reliability of the APACHE II system in the setting of acute pancreatitis has been validated in numerous clinical reports, a value of 8 points or more signifying a severe episode. Recent clinical studies have established an overall clinical accuracy of 80% for APACHE II in predicting the severity of acute pancreatitis. Moreover, the APACHE II system can also be used at any time during the patient’s course, i.e., at onset, day 2, day 5, etc. Finally, by comparing serial determinations of APACHE II, and noting whether the values are increasing or decreasing over time, the efficacy of therapy can also be determined (Fig. 1.1). Despite these obvious clinical advantages over the Ranson Criteria, the principal disadvantage of the APACHE II system is that it is cumbersome, as it requires 15 separate entries (each entry with multiple grades) in order to summate a score. Because of this unavoidable complexity in recording, this system is much better suited to electronic entry in an intensive care environment, or to large-scale clinical investigations, than it is for use in other circumstances.

More recently, other measures of severity have been proposed. Within the past generation, surgical investigators have advanced the proposition that the development of necrotizing pancreatitis is the most significant determinant of the clinical severity of an episode of acute pancreatitis and, indeed, of the prognosis for overall patient survival. These clinicopathologic observations arose from several European surgical clinics, where programmatic surgical resection or débridement was advocated for clinically severe acute pancreatitis. As a result of subsequent worldwide validation of these clinicopathologic observations, methods for the determination of the presence of pancreatic necrosis have received considerable attention as predictors of severity and prognosis (Table 1.1).

The majority of these approaches to the detection of pancreatic necrosis have been biochemical in origin. Despite initial promise, most have proved less reliable than necessary, difficult to perform, time-consuming, or expensive. An exception to this generalization has
the gland, however, the true negative value for CECT has not been established. Clinically, this means that a patient could have a “negative” CT and still have pancreatic necrosis, but its extent would be less than 30% of the gland. This observation fits with modern knowledge regarding histopathology in acute pancreatitis, as microfoci of pancreatic necrosis are the rule in clinical acute pancreatitis, even when coalescence of scattered foci of parenchymal necrosis is insufficient to result in clinical necrotizing pancreatitis.

In addition to the detection of necrosis, tomography-based clinical severity scoring systems using the images obtained from CECT have also been proposed. Although these image-based severity scoring systems are quite useful when comparing groups of patients with necrotizing pancreatitis, they add little to individual

been C-reactive protein (CRP). When associated with the finding of hyperamylasemia in the appropriate clinical setting, a value of 120 mg/dL permits a reasonably secure diagnosis of necrotizing pancreatitis. Although inexpensive to perform, since the CRP test will not normally become positive until 48 hours after the onset of necrotizing pancreatitis, it cannot often be used to make initial clinical decisions.

Today, the test that is widely regarded as the most reliable for the determination of the presence or absence of pancreatic necrosis is contrast-enhanced computed tomography (CECT) (Fig. 1.2). Whenever the nonenhancing segment(s) of the pancreatic parenchyma exceed 30% of the area of the gland, the accuracy of CECT in establishing the presence of pancreatic necrosis exceeds 95%. In the absence of nonenhancement of the gland, however, the true negative value for CECT has not been established. Clinically, this means that a patient could have a “negative” CT and still have pancreatic necrosis, but its extent would be less than 30% of the gland. This observation fits with modern knowledge regarding histopathology in acute pancreatitis, as microfoci of pancreatic necrosis are the rule in clinical acute pancreatitis, even when coalescence of scattered foci of parenchymal necrosis is insufficient to result in clinical necrotizing pancreatitis.

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Figure 1.1 Graphical course of a 57-year-old male patient with severe acute pancreatitis due to sterile pancreatic necrosis. Note that serial APACHE II determinations did not deteriorate after intensive supportive therapy was begun.

Event numbers: 1, contrast-enhanced computed tomography; 2, tracheostomy; *, fine-needle aspiration for bacteriology.
patient management. From a clinical standpoint, it is often sufficient to know that pancreatic necrosis is present in a patient with clinically severe pancreatitis, without the necessity for grading the radiologic appearance. Although CECT scanning is quite accurate for detecting necrosis, it is unfortunately neither inexpensive nor completely risk-free, and is therefore reserved for situations in which it is necessary to definitively establish the presence of necrotizing pancreatitis.

In what circumstances would it be necessary for us to know that a particular episode of clinically severe acute pancreatitis was due to necrotizing pancreatitis? Aside from clinical research requirements or assignment of prognosis, the principal reason is to identify those patients requiring therapy specific for necrotizing pancreatitis. Since as many as 10% of cases of nonnecrotizing acute pancreatitis (interstitial, or edematous, pancreatitis) can also be clinically “severe,” distinction between the two pathologic forms may be necessary. Currently, there are two, perhaps three, major clinical therapeutic decisions which must initially be made in a patient with clinically severe acute pancreatitis: (i) should the patient be admitted to the intensive care unit, (ii) should prophylactic antibiotics be started, and (iii) should an urgent endoscopic sphincterotomy be done? With regard to the first and second questions, knowledge of whether a clinically severe episode of acute pancreatitis is due to pancreatic necrosis is useful for decision-making. Acute interstitial (edematous) pancreatitis never requires prophylactic antibiotics, and less frequently requires intensive care management. Knowledge of the existence of necrotizing pancreatitis is less critical for addressing the question regarding endoscopic sphincterotomy, as this issue revolves principally around demonstrating the existence of necrosis.

Table 1.1 Proposed clinical determinants of necrotizing pancreatitis.

<table>
<thead>
<tr>
<th>Serum factors</th>
<th>Clinical observations</th>
<th>Imaging techniques</th>
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<tbody>
<tr>
<td>Methemalbumin</td>
<td>Grey Turner’s sign; Cullen’s sign</td>
<td>Contrast-enhanced computed tomography*</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fat necrosis</td>
<td>Magnetic resonance imaging*</td>
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<td>( \text{PaO}_2 )</td>
<td>Diagnostic peritoneal lavage</td>
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<td>Lactate dehydrogenase*</td>
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<td>Hypocalcemia</td>
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<td>Ribonuclease I</td>
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<td>Deoxyribonuclease</td>
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<tr>
<td>( \alpha_1 )-Antitrypsin</td>
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<td>( \alpha_2 )-Macroglobulin</td>
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<td>Complement C3 and C4</td>
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<td>C-reactive protein*</td>
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<tr>
<td>Pancreas-specific protein</td>
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<tr>
<td>Phospholipase ( \alpha_1 )</td>
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<tr>
<td>Trypsinogen activation peptide</td>
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<td>Fibronectin</td>
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<td>Polymorphonuclear elastase</td>
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* Author’s choice for easily available and clinically dependable determinants of pancreatic necrosis.
of gallstones associated with cholangitis or biliary obstruction. However, some endoscopists may hesitate to perform sphincterotomy using endoscopic retrograde cholangiopancreatography in patients with documented pancreatic necrosis, fearing that iatrogenic introduction of bacteria might lead to conversion of sterile to infected necrosis.

Furthermore, we can anticipate that, like the ill-fated platelet antagonist factor lexipafant, another agent will be proposed in the not too distant future purporting to ameliorate the clinical course of acute pancreatitis. Since edematous acute pancreatitis resolves with appropriate supportive therapy in the vast majority of cases, employment of an expensive putative therapeutic agent will require prior substantiation of the diagnosis of necrosis before the agent can be given. We can conclude that the more definitive treatments for necrotizing pancreatitis become available in the future, the greater will be the need for establishing severity and detecting necrosis.

Definitions of acute pancreatitis and its complications

Beginning with the Edwin Smith Papyrus (and possibly considerably before), it has been axiomatic in medicine that correct therapy must be preceded by a correct diagnosis. Although other logical combinations exist, such as wrong diagnosis–wrong therapy and correct diagnosis–wrong therapy, patients can only improve with either the serendipitous combination of wrong diagnosis–correct therapy or the more desirable possibility of correct diagnosis–correct therapy. Given the primacy of diagnosis to effective therapy, the necessity for accuracy in diagnosis is clear.

Accuracy in clinical diagnosis, in turn, depends upon a precise and consistent definition for the particular disease process. Without precise definitions, differentiation between closely related disease processes becomes difficult if not impossible. Finally, not only is precision in disease definition required for accurate diagnosis, but in order for the proposed definition to be useful in the clinical situation, a clinical definition must be created that is capable of being determined by clinical means.

We have already noted the clinical difficulties created by an imprecise definition of “pancreatic abscess.” Another case in point is that of “pancreatic phlegmon.” Originally coined in 1973 to describe a sterile mass of inflammatory tissue, subsequent authors embraced the term to describe other forms of pancreatic masses in patients with acute pancreatitis, i.e., necrotic masses, and even infected collections. As a result, “phlegmon” was no longer a specific term used to describe sterile inflammation, but could now improperly refer to any one of four possible combinations (sterile or infected, edema or necrosis), depending upon the views of the author. The persistent use of similarly imprecise definitions resulted in a pancreatic Tower of “Babble.”

For almost 100 years, from the time of the initial pathologic description of acute pancreatitis and its complications by Fitz in 1889 until the advent of noninvasive imaging in the 1980s, progress in the diagnosis and management of pancreatic inflammatory diseases was glacially slow. Not until the technology for noninvasive monitoring became available could the full spectrum of acute pancreatitis and its complications be appreciated in real time, and in the clinical situation. With the new technologies, it was no longer necessary for clinicopathologic correlation to require tissue confirmation from surgical or autopsy specimens; noninvasive data could provide similar information. Indeed, these imaging breakthroughs in the 1980s led to an unmasking of the scope of retroperitoneal mischief caused by pancreatic inflammation, and resulted in a pancreatic renaissance.

In appreciation of the wealth of natural history and clinical information then becoming available, and in recognition of the imprecise and often conflicting definitions in use at that time for acute pancreatitis, an International Symposium on Acute Pancreatitis was convened in Atlanta in 1992. In attendance were 40 internationally recognized experts in acute pancreatitis from 15 countries and six disciplines (pathology, anatomy, radiology, gastroenterology, medicine, and surgery). Their assigned tasks were to provide a series of consensus clinical definitions for acute pancreatitis and its complications, and, where possible, to provide an evidence-based approach to therapy. The clinical definitions proposed, and subsequently adopted by the worldwide medical community, are outlined in Table 1.2 and more fully discussed below.

Acute pancreatitis

Definition
Acute pancreatitis is an acute inflammatory process
of the pancreas, with variable involvement of other regional tissues or remote organ systems.

Clinical manifestations
Most often, acute pancreatitis has a rapid onset, is accompanied by upper abdominal pain, and is associated with variable abdominal findings ranging from mild tenderness to rebound. Acute pancreatitis is often accompanied by vomiting, fever, tachycardia, leukocytosis, and elevated pancreatic enzymes in the blood and/or urine.

Pathology
Findings range from microscopic interstitial edema and fat necrosis of the pancreatic parenchyma to macroscopic areas of pancreatic and peripancreatic necrosis and hemorrhage. These pathologic changes in acute pancreatitis therefore represent a continuum; interstitial edema and minimal histologic evidence of necrosis are at the minor end of the scale, and confluent macroscopic necrosis at the other extreme.

Clinical discussion
Despite all attempts at objectivity, in a small number of patients acute pancreatitis remains a clinical diagnosis. Other causes of hyperamylasemia must be excluded, since significant surgical conditions presenting with hyperamylasemia may clinically masquerade as acute pancreatitis. If clinical doubt exists about whether the abdominal findings are due to acute pancreatitis or are being caused by a correctable intraabdominal catastrophe, CT findings of pancreatic/peripancreatic edema or necrosis are pathognomonic for acute pancreatitis. In the absence of pancreatic/peripancreatic edema, acute pancreatitis is unlikely, and other causes of intra-abdominal disease should be sought.

Severe acute pancreatitis

Definition
Severe acute pancreatitis is associated with organ failure and/or local complications, such as necrosis, abscess, or pseudocyst.

Clinical manifestations
Abdominal findings are of increased tenderness, rebound, distension, and hypoactive or absent bowel sounds. An epigastric mass may be present. Rarely, flank ecchymosis (Grey Turner’s sign) or periumbilical ecchymosis (Cullen’s sign) may be seen. Severe acute pancreatitis is further characterized by either three or more Ranson criteria or eight or more APACHE II criteria. Organ failure is defined as shock (systolic blood pressure $< 90$ mmHg), pulmonary insufficiency ($P_{O2} < 60$ mmHg), renal failure (creatinine $> 2$ mg/dL after rehydration), or gastrointestinal bleeding ($> 500$ mL per 24 hours). Systemic complications, such as disseminated intravascular coagulation (platelets $< 100,000$/mm$^3$, fibrinogen $< 100$ mg/dL, fibrin split products $> 80$ µg/mL), or severe metabolic disturbances (calcium $< 7.5$ mg/dL) may also be seen. Local complications, such as necrosis, abscess, and pseudocyst, are described below.

Pathology
Most often, severe acute pancreatitis is a clinical expression of the development of pancreatic necrosis (see below). Less commonly, however, patients with interstitial (edematous) pancreatitis can also develop clinically severe acute pancreatitis.

Clinical discussion
Severe acute pancreatitis usually declares itself shortly after onset. A delayed progression from mild acute pancreatitis to severe acute pancreatitis is rare. The APACHE II system may be used to quantify severity at any time during the course of acute pancreatitis, while Ranson Criteria have not been validated for time periods longer than 48 hours after onset. Severe acute pancreatitis requires continuous monitoring in an intensive care environment.
Mild acute pancreatitis

Definition
Mild acute pancreatitis is associated with minimal organ dysfunction and an uneventful recovery, and lacks the described features of severe acute pancreatitis.

Clinical manifestations
Patients with mild acute pancreatitis respond to appropriate fluid administration with prompt normalization of physical signs and laboratory values. Failure to improve within 48–72 hours after treatment begins should prompt additional investigations for the presence of complications of pancreatitis. Contrast enhancement of pancreatic parenchyma does not demonstrate necrosis if dynamic computed tomography is performed (see below).

Pathology
The predominant macroscopic and histologic feature of mild acute pancreatitis is interstitial edema, although microscopic areas of parenchymal necrosis may also be found. Peripancreatic fat necrosis may or may not be present.

Clinical discussion
Since the clinical course of acute pancreatitis is uncomplicated in approximately 75% of cases, uneventful recovery with appropriate supportive management can be anticipated. Investigations into the possibility of biliary calculi being the cause of the episode should also be carried out, in order to prevent recurrent acute pancreatitis.

Acute fluid collections

Definition
Acute fluid collections occur early in the course of acute pancreatitis (within the first 2 weeks), are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue.

Clinical manifestations
Acute fluid collections are common in patients with severe pancreatitis, occurring in 30–50% of cases. However, more than half of these lesions regress spontaneously. They are rarely demonstrable by physical findings and are usually discovered by imaging techniques. Imaging techniques do not demonstrate a defined wall surrounding an acute fluid collection, and the collections often have an irregular shape.

Pathology
The precise composition of these acute fluid collections is unknown. Bacteria are variably present. The clinical distinction between an acute fluid collection and a pseudocyst (or a pancreatic abscess) is the lack of a defined wall on imaging studies.

Clinical discussion
Acute fluid collections have the potential to develop into acute pseudocysts or pancreatic abscesses. Why the majority of acute fluid collections regress, while others persist to become pseudocysts or abscesses, is not known. The important point is that continued observation is necessary to determine the direction a fluid collection will take over time.

Pancreatic necrosis

Definition
Pancreatic necrosis is a focal or diffuse area of nonviable pancreatic parenchyma that is typically associated with peripancreatic fat necrosis.

Clinical manifestations
While the likelihood of pancreatic necrosis increases with increasing clinical severity, objective verification is necessary. Dynamic CECT is the current gold standard for the clinical diagnosis of pancreatic necrosis. Focal or diffuse, well-margined zones of nonenhanced pancreatic parenchyma (>3 cm in size or >30% of the area of the pancreas) are requisite criteria for the CT diagnosis of necrosis. Contrast density fails to exceed 50 Hounsfield units (HU) in areas of necrosis after intravenous administration (normal enhancement 50–150 HU). A semiquantitative measure of pancreatic enhancement can be obtained by visually comparing pancreatic density to splenic density, since in the absence of necrosis the densities of the two organs are similar. Heterogeneous densities demonstrated in the peripancreatic fat represent a combination of fat necrosis, fluid collections, and hemorrhage. As a result, the extent of peripancreatic fat necrosis cannot be reliably determined by CT. Although the overall accuracy of dynamic CT in demonstrating parenchymal pancreatic necrosis is 95%, this technique should not be considered infallible. Pancreatic necrosis may also be reliably
determined by magnetic resonance imaging, although at a considerable increase in cost.

Pathology
Macroscopically, focal or diffuse areas of devitalized pancreatic parenchyma and peripancreatic fat necrosis are evident. Fat necrosis may be superficial and patchy, or deep and confluent. Hemorrhage in the pancreatic or peripancreatic tissues is variably present. Microscopically, extensive interstitial fat necrosis with vessel damage is found, along with necrosis that affects acinar cells, islet cells, and the pancreatic ductal system. Pancreatic parenchymal necrosis rarely involves the entire gland, however. Usually, pancreatic necrosis is confined to the periphery, and the central core of the gland is preserved. Uncommonly, peripancreatic fat necrosis may become loculated, and is often misdiagnosed as a pseudocyst or a sterile abscess. Loculated fat necrosis can be differentiated from a pancreatic pseudocyst by the demonstration of thick viscous contents without pancreatic enzymes, and from a pancreatic abscess by the absence of bacteria.

Clinical discussion
The clinical distinction between sterile pancreatic necrosis and infected pancreatic necrosis is critical, since development of infection in the necrotic tissues results in a trebling of mortality risk. Furthermore, while selected patients with documented sterile pancreatic necrosis can usually be managed without surgical intervention, infected necrosis is uniformly fatal without surgical drainage. Because clinical and laboratory findings are often similar in patients with either sterile or infected necrosis, this important distinction is best made by transcutaneous needle aspiration bacteriology. This technique is safe and accurate, and a positive result is regarded as an indication for surgery.

Acute pseudocyst
Definition
A pseudocyst is a collection of pancreatic juice enclosed by a nonepithelialized wall, which arises as a consequence of acute pancreatitis, pancreatic trauma, or chronic pancreatitis.

Clinical manifestations
Pseudocysts in patients with acute pancreatitis are rarely palpable, and are most often discovered by imaging techniques. It is important to note that they are round or ovoid in shape, in contrast to acute fluid collections, and have a well-defined wall, as demonstrated by CT or sonography.

Pathology
The presence of a well-defined wall composed of granulation or fibrous tissue distinguishes a pseudocyst from an acute fluid collection. A pseudocyst is usually rich in pancreatic enzymes, and is most often sterile.

Clinical discussion
Formation of a pseudocyst requires 4 weeks or more from the onset of acute pancreatitis. In this regard, an acute pseudocyst is a fluid collection that arises in association with an episode of acute pancreatitis, is of more than 4 weeks’ duration, and is surrounded by a defined wall. Fluid collections less than this age that lack a defined wall are more properly termed acute fluid collections. In contrast, chronic pseudocysts have a well-defined wall, but arise in patients with chronic pancreatitis and lack an antecedent episode of acute pancreatitis. Bacteria may be present in a pseudocyst, but often are of no clinical significance, since they represent contamination and not clinical infection. If purulent material is present, the lesion is more correctly termed a pancreatic abscess.

Pancreatic abscess
Definition
A pancreatic abscess is a circumscribed intra-abdominal collection of pus in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma.

Clinical manifestations
Clinical presentation is variable. Most commonly, however, the clinical picture is that of infection. Pancreatic abscesses occur later in the course of severe acute pancreatitis, often 4 weeks or more after onset.

Pathology
The presence of pus and a positive culture for bacteria or fungi, but little or no pancreatic necrosis, serves to differentiate a pancreatic or peripancreatic abscess from infected necrosis. Pancreatic abscesses probably arise as a consequence of limited necrosis with subsequent liquefaction and secondary infection. Accord-