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Biochemical Indicators of Acute Pancreatitis

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INTRODUCTION

One of the earliest biochemical markers employed for the diagnosis of a particular disease state was reported in 1916 by Stocks *(1)*, who suggested that amylase activity in blood and urine was a sensitive and reliable test for various pancreatic disorders. Since this time, numerous other enzymatic markers of pancreatic disease have been described. Although there is a large body of literature indicating that some of these other tests may provide better diagnostic accuracy of acute pancreatitis when compared with serum amylase, none of these newer tests have replaced amylase. Amylase remains among one of the top 20 most frequently requested clinical assays and is an important component of emergency laboratory services *(2)*. Recent studies, however, have demonstrated that other markers in addition to amylase offer greater clinical specificity for the diagnosis of acute pancreatitis and should replace amylase as the primary test for this disease. As stated by Tietz, "old myths die hard" *(3)*. It will probably take years before the diagnostic utility of these other tests are recognized. This section reviews the diagnostic utility of both the commonly used and more esoteric indicators of acute pancreatitis. The analytes most frequently employed for the diagnosis of acute pancreatitis include amylase and the pancreatic isoenzyme of amylase and lipase. The markers infrequently used, but that may provide good diagnostic and/or prognostic information, include trypsin, phospholipase A (PLA), carboxypeptidase A, and lipase isoforms. Also discussed are some key issues related to the correct interpretation of these tests in certain pathophysiological states such as renal failure. In addition, the utility of some of these studies in the investigation of the etiology of an attack of acute pancreatitis is also reviewed.

AMYLASE

Measurement of serum amylase has long been considered the test of choice in the evaluation of patients with suspected acute pancreatitis. Amylase activities rise within the first 12–24 h following an attack of acute pancreatitis and then decline steadily to normal values over the next 4–7 d. Since amylase is eliminated via renal excretion, patients with impaired renal function may exhibit longer elimination times for the enzyme.

Amylase has widespread acceptance by clinicians for the diagnosis of pancreatic disease. The test can be performed inexpensively and rapidly using instrumentation

From: Clinical Pathology of Pancreatic Disorders *Edited by: J. A. Lott Humana Press Inc., Totowa, NJ*

available in most hospital laboratories. Unfortunately, however, the specificity of amylase for the pancreas is poor. Amylase is found in a number of tissues in addition to the pancreas, including the salivary glands, fallopian tubes, and small intestine. Thus, patients presenting with abdominal pain and increased amylase activities in serum may not have pancreatitis. Instead these patients may have hyperamylasemia secondary to intestinal obstruction or ischemia, or disorders affecting the fallopian tubes. It is important to differentiate acute pancreatitis from these other disorders owing to differences in treatment modalities. Patients with the benign condition of macroamylasemia, in which amylase is bound to serum immunoglobulins, may present with greatly increased serum amylase activities, but without other signs or symptoms suggestive of pancreatitis. The incidence of this disorder has been estimated to be 0.5–2.0% of the general population. The combination of immunoglobulin and enzyme results in the formation of a protein complex that is too large to be cleared by the kidneys, and may also prevent or delay elimination via the reticuloendothelial system. Determination of the amylase:creatinine clearance ratio can help in the identification of hyperamylasemia owing to macroamylasemia. However, the amylase:creatinine clearance ratio does not offer any advantage over serum amylase in the diagnosis of acute pancreatitis and should be abandoned for this purpose *(4)*. In addition to the high rate of false-positive test results obtained using serum amylase activity, the finding of acute pancreatitis and normal amylase activities is common *(5)*. Patients with acute pancreatitis owing to ethanol abuse may present with normal or just mild increases in serum amylase activities.

The nonspecificity of amylase for the pancreas can be overcome by analysis of amylase isoenzymes. Amylase seen in many of the disease states causing an increase in serum amylase activities is usually owing to increases in the salivary isoenzymes. The pancreas has the highest concentration of amylase per gram of tissue, and also contains the greatest total amount of amylase relative to any other amylase-containing organ in the body. Amylase is not absorbed by intact gut mucosa. Thus, normal serum concentrations of amylase are derived from leakage of the enzyme into the blood from the pancreatic acinar cells, or via lymphatic drainage from the pancreas or salivary glands. Obstruction of the pancreatic ducts or pancreatic inflammation results in increased cellular enzyme leakage into the blood or the lymphatics. Disorders, which cause an increase in the permeability of the gut mucosa, or cases whereby perforation or rupture of the gastrointestinal tract occurs, may result in the release of large quantities of fluid into the peritoneal or pleural space. This fluid containing large amounts of amylase is eventually drained via the lymphatics into the systemic circulation causing hyperamylasemia *(6)*.

Since the pancreas contains the highest concentration of enzyme per gram of tissue, and is the largest organ containing amylase, acute pancreatitis should result in the greatest increase of enzyme activity in the blood when compared with other disorders associated with increased amylase activity. Many studies have cited the sensitivity and specificity of amylase for acute pancreatitis to be well over 90% when interpreted in conjunction with an appropriate clinical picture *(7,8)*. These values are usually obtained using amylase cutoff values that are four to five times the upper range of the normal reference interval. Thus, when using the Phadebas method for amylase, which has a normal reference interval of 70–300 U/L, many authors consider amylase val-

ues of at least 1000–2000 U/L to be diagnostic of acute pancreatitis *(9,10)*. Other studies indicate that amylase is diagnostic of acute pancreatitis when values exceed 2 to "several times" the upper reference interval *(11)*. However, many studies base sensitivities and specificities of amylase for acute pancreatitis on values that exceed the upper range of the normal reference interval only.

Since the diagnostic criteria for acute pancreatitis are loosely defined, a wide range of sensitivities and specificities for amylase have been reported. Another factor influencing these parameters is the use of initial or peak enzyme activities when evaluating the diagnostic performance of these markers. One common approach used in assessing the diagnostic accuracy of amylase and lipase is to evaluate these markers using peak enzyme activities selected retrospectively from serial measurements. However, this type of evaluation of the diagnostic utility is unrealistic; the diagnosis of a life-threatening event, such as acute pancreatitis, requires that medical decisions be based on enzyme findings obtained at admission or early in the course of the disease. The use of peak enzyme data usually leads to falsely increased claims for sensitivity and specificity of the test. Use of peak data may also change the optimal decision threshold of the marker, compared with evaluations based on enzyme data obtained at admission. Use of enzyme data at admission may result in lower reported test sensitivity because of the time delay between the onset of clinical symptoms and appearance of abnormal concentrations in the blood.

A number of studies have challenged the primary diagnostic role of amylase for acute pancreatitis. Many have advocated the use of serum lipase as the primary biochemical test for this disease. In addition, assays for a variety of other pancreatic enzymes, including trypsin, phospholipase A, elastase, and carboxypeptidase, have been developed in order to improve the biochemical diagnosis of acute pancreatitis. However, recent data suggest that when appropriate cutoff intervals are used, the amylase activity obtained at admission may have a diagnostic accuracy for acute pancreatitis equivalent to other available biochemical markers *(8,12,13)*. One recent study evaluated initial, peak, and serial amylase and lipase activities for the diagnosis of acute pancreatitis using a multivariate data approach *(13)*. Analysis of enzyme data by use of a multivariate technique permits a more accurate and unbiased assessment of test utility, because patients can be classified with respect to disease status by use of all available enzyme data. Multivariate approaches, such as those that employ neural networks, classify patients with respect to disease status on the basis of the diagnostic patterns in amylase and lipase that may be subtle and not readily appreciated by human observation. Analysis of both amylase and lipase obtained from over 500 patients has shown that when peak enzyme activities are used for evaluating the diagnostic accuracy of these enzymes, lipase shows significantly better diagnostic utility *(13)*. However, when initial enzyme activities are considered only, no significant difference in diagnostic accuracy between amylase and lipase can be demonstrated. These differences in diagnostic accuracies obtained using either initial or peak enzyme activities may help explain much of the controversy in the literature surrounding the relative merits of amylase vs lipase.

However, evaluation of serial amylase and lipase data by use of neural network analysis reveals significantly better diagnostic utility for lipase than for amylase when serial enzyme data are considered *(13)*. Diagnosis of acute pancreatitis by use of a

neural network that used serial lipase data showed greater diagnostic accuracy for acute pancreatitis than either initial, peak, or serial amylase activity. A major limitation of data analysis using neural networks is that rules and representations that the system develops during the process of data evaluation are not readily available to the user. Almost all understanding of the functioning of the neural network comes from observation of the data input into the system (i.e., serial amylase or lipase results) and how the system assigns patients with respect to disease status. In addition, although the neural network may identify patterns in the data that may be useful for the diagnosis of acute pancreatitis, these patterns may not be apparent to the user of the system.

Controversy still exists regarding the diagnostic information gained from the simultaneous measurement of amylase and lipase vs measurement of either enzyme alone. Previous work using a neural network approach showed that serial amylase and lipase measurements did not provide greater diagnostic accuracy for pancreatitis when compared to serial lipase measurements alone *(13)*. However, amylase in conjunction with lipase provided significantly better diagnostic accuracy compared to serial amylase measurements. Another recent study addressing this issue evaluated the initial amylase and lipase results using "AND" and "OR" rules and discriminant function analysis *(12)*. This approach also demonstrated that combinations of both amylase and lipase offer no advantages over using lipase results alone. However, use of a logistic regression discriminant function was found to offer statistically significant superior performance over lipase alone. The successful clinical application of such an approach would necessitate the formulation of a discriminant function rule specific to the particular local population of patients and analytical techniques used for measuring amylase and lipase activity.

Amylase Isoenzymes

The recognization that amylase is produced by multiple tissues, in addition to the pancreas, requires that extreme caution be used in the interpretation of abnormal amylase activities. Whereas an increased serum amylase activity may be a very sensitive indicator of pancreatic injury, the marker suffers from lack of specificity. Hyperamylasemia has been associated with several nonpancreatic disorders that may mimic clinical pancreatitis. These include ruptured ectopic pregnancy, perforated peptic ulcer, appendicitis, choledocholithiasis, and mesenteric artery infarction *(14)*. The vast majority of patients presenting with abdominal pain suggestive of acute pancreatitis and an abnormal value for serum amylase activity will be assigned a diagnosis of acute pancreatitis. However, one study found that only one-third of such patients actually had pancreatitis *(15)*. Patients presenting with abdominal pain associated with alcohol use and who show an abnormally increased serum amylase may be overdiagnosed with acute pancreatitis to an even greater extent. Only 15% of patients of patients falling into the aforementioned category were actually found to have biochemical evidence of acute pancreatitis *(16)*. The use of total amylase only in the evaluation of patients with suspected acute pancreatitis is associated with a high rate of overdiagnosis of the disease. In addition, some patients with acute pancreatitis may present with normal or just mild increases in amylase activity. Although this situation occurs infrequently, it may be seen in patients who present several days after the onset of the disease when

amylase activities have declined back into the normal range. In these patients, underdiagnosis of acute pancreatitis is possible.

Attempts to improve the specificity of serum amylase for the diagnosis of acute pancreatitis have led to the development and use of the amylase:creatinine clearance ratio, and the determination of amylase isoenzymes by a variety of methods, including electrophoresis, inhibition of the salivary isoenzyme with use of lectins, and immunoinhibition methods with use of monoclonal antibodies (MAbs) directed against the salivary isoenzyme.

Amylase in serum can usually be separated by electrophoresis into two major fractions termed salivary (S) or pancreatic (P). In turn, each S- and P-type isoenzyme fraction may show three distinct isoform fractions. Three pancreatic isoforms (P_1, P_2, P_3) and three salivary isoforms (S_1, S_2, S_3) may be seen. Except for the P_1 isoform fraction, which is thought to represent a genetic variant, all the other amylase isoforms are produced as a result of posttranslational modification of the P_2 and S_1 forms *(17)*. In patients with acute pancreatitis, the typical findings include a dominant increase in total P-type isoenzyme fraction. This increase can be noted by visual or densitometric review of the electrophoretic gel or by increases in P-type activity measured using quantitative methods.

Detection of the P_3 isoform following electrophoretic separation of amylase has been advocated as a specific marker of acute pancreatitis. This fraction is presumed to occur in patients with acute pancreatitis owing to intrapancreatic proteolytic modification of the other pancreatic isoform fractions. However, the P_3 isoform has been shown to be present in approx 40% of patients with chronic renal insufficiency, limiting its usefulness in this patient population *(18)*. False-positive findings for the P_3 isoform have also been reported in patients with biliary tract disease and in patients with necrosis of the bowel *(19)*. The mechanism by which P_3 is produced in these other disease states is not clear. It has been previously suggested that the P_2 isoform released from the biliary tract or bowel could be modified to produce the P_3 isoform. Although the P_3 isoform may be observed in patients with renal insufficiency or abdominal pain owing to causes other than pancreatitis, the absence of the P_3 isoform virtually excludes a diagnosis of acute pancreatitis.

The determination of the P_3 isoform is further hampered by the fact that its presence on electrophoretic gels is often masked by the S_1 isoform. Insufficient separation of the S_1 and P_3 isoform often does not permit the quantitation of either isoform by densimetric methods. A method used to determine the presence of P_3 accurately has been developed *(20)*. The method developed to measure the P_3 isoform more accurately is the P_3 index. The P_3 index is a measure of the ratio of the P_3 isoform to the S_1 isoform. Normal patients and those with abdominal pathology mimicking pancreatitis, but who do not have the disease typically show a P_3 index >80%.

The P_3 index was developed following early observations that the distance of electrophoretic migration between the main pancreatic isoform, P_2, and the next anodal fraction, P_1, is approx 60% of the distance between the P_2 and S_1 isoform peaks obtained using a standard solution *(20)*. The standard solution is prepared from salivary gland and pancreatic tissue. As a patient with pancreatitis recovers, the distance between the P_2 and P_1 peak increases, and this increase is owing to the gradual disappearance of the P_3 isoform. The P_3 index is calculated as follows:

$$P_3 \text{ index } (\%) = (\text{Distance between } P_2 \text{ and } P_1/\text{Distance between } P_2 \text{ and } S_1) \times 100 \quad (1)$$

Early studies on the diagnostic utility of the P_3 isoform indicated that its determination of this marker may provide better diagnostic accuracy for acute pancreatitis than total amylase or lipase activities *(21)*. However, later studies using greater numbers of patients with a variety of abdominal disorders showed that the P_3 isoform has the same diagnostic accuracy for acute pancreatitis as lipase *(19)*. Use of both the P_3 isoform and lipase in combination does not provide any additional diagnostic information compared with single enzyme determinations.

Similar diagnostic accuracy has also been noted between total pancreatic isoamylase and lipase activities for acute pancreatitis. When appropriate reference cutoffs are applied, lipase and pancreatic amylase demonstrate diagnostic efficiencies of 0.94 and 0.93, respectively *(22)*. The importance of utilizing appropriate reference cutoffs for these indicators of pancreatitis deserve special emphasis. Several investigators describe a "gray zone" that lies between the upper normal reference interval and the cutoff value, which provides the greatest diagnostic efficiency as determined by receiver operator characteristic curve analysis. Recent studies have shown that this "gray zone" is approximately four to five times the upper limit of the normal reference interval *(19,22)*.

In summary, it has been readily shown that total pancreatic amylase activity and the P_3 isoform fraction are equivalent to total lipase activity for the diagnosis of acute pancreatitis. Determination of the P_3 isoform by electrophoretic separation of the various amylase isoforms is both labor-intensive and not amendable to the rapid reporting of test results; these factors severely limit its clinical utility *(23)*. Rapid and accurate measurement of the total pancreatic isoamylase fraction can be readily accomplished with automated immunochemical techniques employing MAbs.

LIPASE

Pancreatic lipase is often considered to be a more sensitive and specific marker for acute pancreatitis compared with total amylase. Until relatively recently, lipase was infrequently requested by clinicians. The test has a long history of being difficult to perform and having poor precision. However, most commercially available assays for lipase now incorporate the important cofactor called colipase. Colipase is present in the blood of patients with pancreatitis, but in concentrations that are highly variable and usually well below what is required to activate pancreatic lipase fully *(24)*. Thus, the addition of colipase has greatly improved the diagnostic utility of lipase on both analytical and clinical grounds. Extremely abnormal lipase values appear to be pathognomonic for pancreatitis. In assays that utilize the colipase cofactor, the increase in lipase is much more pronounced yielding greater diagnostic power of the test.

Early reports on lipase indicated that the enzyme became increased in serum following increases in amylase and returned to within the normal reference interval before amylase. However, recent studies using lipase measured by procedures containing the colipase cofactor suggest that lipase increases sooner, and remains increased longer than amylase *(25)*. The magnitude of increase in lipase above the upper reference limit in patients with acute pancreatitis can vary dramatically depending on what analytical assay is utilized for its measurement. Discrepancies as great as 13 times the

upper reference limit cutoff have been observed among the various assays *(26)*. Although results between different assays may correlate, the presence of a strong correlation between different assays does not mean that identical diagnostic accuracies exist between the different methods. For lipase, marked differences in catalytic activity may be observed between the different analytical assays that are available. These differences may have profound effects on the diagnostic accuracy that can be achieved.

Much has been written on the diagnostic utility of lipase vs that of amylase. This topic has been addressed in the Amylase section of this chapter. Recent studies have attempted to utilize the differences in the serum activities of amylase and lipase in order to distinguish among the different causes of pancreatitis, specifically pancreatitis owing to ethanol abuse and pancreatitis owing to biliary obstruction *(27,28)*. The amylase response in patients with acute pancreatitis has been noted, in general, to be lower in ethanol-induced pancreatitis compared to other pathogenesis. It has been suggested that the smaller increase in amylase in patients with ethanol-induced pancreatitis is owing to a chronically diseased pancreas and little amylase reserve in the gland. However, patients with ethanol-induced pancreatitis can produce significant increases in serum lipase activities similar to those observed in patients with pancreatitis owing to other causes *(27)*. This finding does not lend support to the suggestion that a chronic insult to the pancreas owing to repeated ethanol ingestion causes a selective decrease in pancreas amylase activities. Other mechanisms have been proposed to explain the difference in amylase activities seen in alcoholic vs nonalcoholic acute pancreatitis. A difference in the mechanism by which amylase and lipase reach the blood following pancreatic injury might be different in the alcoholic vs the nonalcoholic patient *(27)*. It should be noted however that the clinical utility of the ratio of lipase activity to amylase activity as a means for distinguishing acute pancreatitis owing to ethanol abuse from acute pancreatitis owing to other pathogenesis is still under investigation. Some studies have found this ratio not to be useful in determining the pathogenesis of the disease *(29)*.

The early discrimination of biliary obstruction and acute pancreatitis from pancreatitis owing to other causes, such as ethanol, is essential owing to differences in management of those with biliary pancreatitis. Patients with acute pancreatitis owing to biliary obstruction may be at greater risk for the evolution of pancreatic edema to hemorrhage and necrosis. Persistent ampullary obstruction has been shown to increase the severity of the attack. Thus, a rapid and noninvasive method for differentiating patients with pancreatitis owing to biliary obstruction from other causes has gained considerable interest. In addition to the ratio of lipase to amylase, other markers that have been evaluated for determining the pathogenesis of acute pancreatitis include aspartate and alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and total bilirubin.

Obstruction of the biliary tract causes a rapid increase in pressure within the bile duct with consequent liver cell damage, and release of aspartate and alanine transaminase. Increases in alkaline phosphatase and total bilirubin have also been noted, although significant increases in these tests may not occur if the bile duct is obstructed only transiently. Following passage or removal of the obstruction, a sudden decrease in biliary pressure occurs with rapid normalization of enzyme activities in serum. The rapidity and transient nature of enzyme changes seen in patients with pancreatitis

owing to biliary obstruction make it imperative that frequent serial determinations of these analytes be performed. It has been demonstrated previously that aspartate and alanine aminotransferase, as well as amylase may decrease from peak activities that are 10–15 times the upper reference interval to within the normal reference interval within 24 h following removal of a gallstone that has been obstructing the biliary passages *(28)*. The speed by which these enzyme changes occur may explain why some studies fail in their attempts to utilize biochemical markers for the determination of the pathogenesis of acute pancreatitis *(29,30)*.

One recent study that evaluated a series of different biochemical markers for determining the pathogenesis of acute pancreatitis found that alanine aminotransferase was the best test for correctly identifying patients with acute pancreatitis resulting from biliary obstruction from those with pancreatitis owing to other causes *(28)*. In addition to alanine aminotransferase, the only other test that could discriminate biliary from other causes of acute pancreatitis was the ratio of lipase to amylase.

Lipase Isoforms

Measurement of isoenzymes or isoforms of enzymes (e.g., creatinine kinase, lactate dehydrogenase, amylase) can provide diagnostic information that has greater utility than that provided by the total enzyme activity. Pancreatic lipase isoforms have recently been shown also to provide diagnostic information that is much better than that provided by total enzyme activity *(31)*. Pancreatic lipase consists of at least three isoforms that can be separated by electrophoresis. The three lipase isoforms present in pancreatic fluid include L1 and L2, which appear to be pancreatic lipase owing to their reactivity with human antipancreatic lipase antibody. The third isoform, L3, is believed to be cholesterol esterase. The L1 and L2 isoforms are probably posttranslational variants of a single enzyme form. Previous work has shown that human pancreatic juice contains two pancreatic isolipases having isoelectric pHs of 5.80 and 5.85 *(32)*. No immunological differences between the L1 and L2 forms have been shown. It has been speculated that the L2 isoform represents a (pro) colipase complex released from the injured pancreas. Ordinarily, colipase is undetectable in serum because it is presumed to be cleared rapidly from the circulation *(33)*. Detection of an activated form of colipase within this complex may be useful in predicting the presence of peripancreatic fat necrosis or the development of systemic complications related to lipolysis *(34)*. Further work in increasing the current understanding of lipase isoforms and their diagnostic as well as prognostic utility is needed.

The L2 lipase isoform has been shown to have a sensitivity of 100% in patients with acute pancreatitis *(31)*. However, up to 70% of patients with disorders involving the liver or biliary tract have been found to contain the L2 isoform in serum. This finding has been suggested to be the result of extreme sensitivity of the pancreas to inflammation of nearby organs. For the diagnosis of acute pancreatitis, total lipase and the L2 isoform show essentially the same diagnostic sensitivity, although the diagnostic accuracy of L2 appears to be better *(31)*.

TRYPSIN

Trypsin is produced primarily by the pancreas; a very small amount is found in Paneth cells in the intestine *(35)*, and its measurement should provide a specific

diagnosis of acute pancreatitis. Once released into the serum, trypsin is immediately complexed by its two main protease inhibitors, α-2-macroglobulin and α-1-protease inhibitor. The majority of the trypsin–α-2-macroglobulin complexes are quickly metabolized by the reticuloendothelial system. Immunoassays developed to quantitate trypsin measure primarily circulating trypsinogen or the α-1-protease inhibitor complexes. Thus, immunoassays fail to differentiate between active enzyme (trypsin) and the parent zymogen (trypsinogen). Specific identification of the α-1-protease inhibitor–trypsin complex in serum may help in the identification of patients with acute, severe pancreatitis who have had release of active protease enzymes into the circulation. Assays that measure both the active and inactive enzyme do not allow this. Thus, the current immunoassays that measure all forms of the enzyme are probably not better at diagnosing acute pancreatitis compared to the standard enzyme assays, such as amylase or lipase.

The recent development of an assay that measures α-2-macroglobulin–trypsin complexes only has been shown to be useful for diagnosing pancreatitis owing to ethanol from pancreatitis resulting from other causes *(36)*. Patients with pancreatitis due to causes other than ethanol were found to have no increase in serum trypsin activity, whereas high concentrations of active trypsin were found in patients with acute alcoholic pancreatitis.

The mechanism by which ethanol-induced pancreatitis causes increased serum trypsin concentrations is not known. Chronic consumption of ethanol can increase the synthesis of trypsinogen, resulting in greater concentrations of the enzyme in pancreatic juice than is found in nondrinkers of ethanol. Another reason may be owing to decreased clearance of the α-2-macroglobulin–trypsin complex by the reticuloendothelial system resulting from ethanol. Further investigation validating these initial studies is warranted.

Another assay designed to measure the amount of trypsinogen that becomes activated in acute pancreatitis utilizes antibodies directed against the C-terminal end of trypsinogen activation peptide. This peptide is produced following activation of trypsinogen to trypsin. The trypsinogen activation peptide is excreted rapidly in the urine. Its measurement in the urine thus provides a useful way for gauging the amount of trypsinogen that has been activated. Peak urinary concentrations of trypsinogen activation peptide occur between 12 and 24 h following the onset of symptoms. Concentrations are much greater in patients with severe disease compared to those with mild disease. Since trypsin can activate proPLA to PLA, it has been suggested that severe acute pancreatitis results from the activation of proPLA by trypsin *(37)*.

PHOSPHOLIPASE A

PLA has been recommended as a useful marker for gauging the severity of acute pancreatitis *(38)*. The enzyme is secreted by the pancreas in an inactive form, and activation by trypsin follows proteolytic cleavage of an activation peptide. Circulating active PLA is thought to attack phospholipids in cells and lung surfactant leading to the development of systemic complications *(39)*. The activity of PLA in serum has therefore been advocated as an indicator of disease severity; greatly increased concentrations are associated with severe hemorrhagic forms of the disease and lesser increases are found in the mild edematous types.

A number of different assays have been developed for the measurement of PLA. Radioimmunological procedures measure concentration of the enzyme, and these values most closely parallel the course of amylase and lipase activity in patients with acute pancreatitis *(40)*. Enzymatic assays have also been developed, and they measure enzyme activity based on the liberation of fatty acids from phospholipid substrates. Catalytic activity of PLA does not necessarily correlate with amylase or lipase activities. This finding has been suggested to indicate that increases in PLA found in patients with necrotizing pancreatitis are not pancreas-derived. Many studies have reported increased PLA activities in association with a wide variety of nonpancreatic disorders including sepsis, malignancy, myocardial infarction, and hematological diseases *(39,41)*.

Recent investigations into the diagnostic and prognostic utility of PLA activity suggest that measurement of catalytic enzyme activity is not always useful in patients with acute pancreatitis *(42)*. Enzyme values were found to be markedly increased in a wide variety of conditions not involving the pancreas. Substantial concentrations of PLA have also been found in leukocytes, and activation of those cells with release of active enzyme into the circulation may explain the increased PLA activities seen in patients with nonpancreatic inflammatory diseases. In addition, association has been demonstrated between an increase in mortality and increased PLA catalytic activity *(41)*. This finding is consistent with the assertion that the significant increases in PLA in serum seen in patients with severe forms of acute pancreatitis are not necessarily derived from the pancreas. Any increase in PLA activity usually occurs late in the course of the disease after the clinical course of the patient has deteriorated considerably.

CARBOXYPEPTIDASE A

Carboxypeptidase A is a pancreatic enzyme that cleaves carboxy-terminal amino acids from proteins. The enzyme shows dramatic increases in the serum following the onset of acute pancreatitis *(43)*. Substantial carboxypeptidase A activity is found in the pancreas with minor amounts (<1% of that found in pancreas) found in intestinal tissue *(43)*. When compared with amylase and lipase, carboxypeptidase A is the most tissue-specific enzyme. Patients with pancreatitis show much greater increases in carboxypeptidase A activity above the upper reference interval compared with amylase and lipase. Mean peak amylase, lipase, and carboxypeptidase A activities in patients with pancreatitis were found to be 9, 23, and 40 times the upper reference limit, respectively. Carboxypeptidase A also increases faster than and remains increased longer than amylase or lipase in patients with pancreatitis.

Techniques developed for measurement of carboxypeptidase A include quantitation of L-phenylalanine released from the substrate by use of affinity chromatography *(44)* and an automated colorimetric method *(45)*. Although the colorimetric method is simple to perform and adaptable to automation, the procedure is subject to severe negative interference by glucose and bilirubin. At bilirubin concentrations of only 30 mg/L, carboxypeptidase A activity is decreased to one-half of its original activity. Glucose concentrations >2000 mg/L show similar negative effects. The effect of these interferents can be eliminated by substitution of an enzymatic, kinetic reaction for the colorimetric indicator reaction *(43)*.

Comparison of the diagnostic utility of carboxypeptidase A with that of amylase and lipase shows that all three enzymes exhibit similar diagnostic accuracies. Although

carboxypeptidase A is more specific for the pancreas than amylase or lipase, the presence of renal insufficiency leads to much more frequent increases in the serum activity of this marker when compared with amylase or lipase. The molecular mass of carboxypeptidase A is 35,000 Da, which is less than that of amylase (50,000 Da) and lipase (38,000 Da). Currently, the routine application of carboxypeptidase A measurements for the evaluation of acute pancreatitis is probably not warranted.

ETIOLOGY OF ACUTE PANCREATITIS

Acute pancreatitis can present with a wide spectrum of signs and symptoms ranging from mild discomfort to severe prostration with multiple organ failure. The variability in the presentation of acute pancreatitis and its clinical course has necessitated the establishment of classification schemes in order to provide a basis for the study and treatment of acute pancreatitis and its complications *(46)*.

Throughout the years a number of classification systems have been proposed. Early systems were based primarily on clinical criteria, and classified pancreatitis into acute and chronic forms of the disease. Further expansion of this system gave rise to a third category, chronic relapsing pancreatitis, that was later broadened to cover the wide variety of clinical presentations ranging from painless presentation to the severe fatal form of the disease. Although this classification scheme is easily implemented, it does little to identify the etiologic factors responsible for the development of the disease. In particular, it does not allow an appreciation for the natural course of the disease and the diagnostic and therapeutic aspects that the various etiologies of the disease entail. Identification of the etiology of an attack of acute pancreatitis is essential to prevent recurrences and possible complications. It was only natural that the clinical classification schemes give rise to classification schemes based on etiologic factors. The etiologic factors that have been implicated in the pathogenesis of acute pancreatitis are numerous and varied. A recent review of the subject lists close to 70 conditions that have the potential of initiating acute pancreatitis *(47)*. Unfortunately, given the great number of recognized etiological factors, little is known about the actual mechanisms by which these factors precipitate acute pancreatitis. The etiologic categories can be defined under the general headings of pancreatic duct obstruction, drugs and toxins including ethanol, metabolic causes, trauma, including postsurgical and blunt force, anatomic abnormalities, and idiopathic.

Drugs and Toxins

Reports of drug-induced pancreatitis first appeared in the mid- to late 1950s, when it was noted that cortisone and thiazides could induce acute pancreatitis *(48,49)*. Since then, published reports have identified approx 50 drugs that may be directly responsible for inducing acute pancreatitis *(50)*. The incidence of drug-induced pancreatitis is estimated at $<2\%$ *(50)*. A higher incidence has been observed in patients with diseases usually associated with acute pancreatitis. Thus, patients with pre-existing inflammatory bowel disease may experience drug-induced pancreatitis at a rate two to three times greater than that seen in patients without inflammatory bowel disease.

Little information is available concerning the pathogenesis or dose relationship between certain drugs and pancreatitis. For some drugs, a slight relationship has been shown between drug use and the onset of pancreatitis, whereas for others, a very

strong association exists. Drugs associated with pancreatitis may be classified into one of three groups: definite association with pancreatitis, possible association, and drugs proposed as causing pancreatitis, but documented evidence for a causal relationship is lacking *(51)*.

Drugs reported to show a definite association with pancreatitis include azathioprine, chlorothiazide, estrogens, furosemide, sulfonamides, tetracycline, and valproate. For all these compounds, pancreatitis develops in some patients taking the drug and disappears following drug withdrawal. In many cases, pancreatitis again develops following reintroduction of the drug. Additional evidence has been obtained from studies of the incidence of pancreatitis in treated and untreated control populations and studies in control and experimental animals given the drug.

Drugs for which an association with pancreatitis is thought to exist include L-asparaginase, corticosteroids, ethacrynic acid, phenformin, and procainamide. For many of these drugs, pancreatitis developed in patients who frequently had serious underlying disease and were on a regimen of multiple drugs. For some compounds, it is often difficult to show a direct relation between a particular drug and pancreatitis owing to these confounding factors.

The majority of drugs fall into the category of "proposed as causing pancreatitis, but lacking in strong documented evidence." Drugs falling into this category include amphetamines, cholestyramine, propoxyphene, histamine, indomethacin, isoniazid, mercaptopurine, opiates, rifampicin, salicylates, cimetidine, and acetaminophen. At present, further documented information regarding the relationship between these drugs and pancreatitis is needed.

Pancreatitis in association with HIV infection with or without the acquired immunodeficiency syndrome (AIDS) has been reported with increasing frequency over the past several years. Acute pancreatitis was once considered to be uncommon in AIDS patients; however, recent studies indicate an increasing incidence of pancreatitis of up to 30% *(52)*. Autopsy studies in patients with AIDS indicate abnormalities in the pancreas in up to 50% *(53)*. Pathologic changes include pancreatic inflammation, fibrosis, and hemorrhage. Opportunistic infection may affect the pancreas in 10% of these individuals.

Biochemical abnormalities in patients with AIDS, such as hyperamylasemia, and hyperlipasemia are frequently found. Up to half of these patients may demonstrate enzyme abnormalities, but otherwise appear asymptomatic; the amylase in these patients is frequently of salivary origin *(52)*. Even though these patients may appear asymptomatic, the finding of increased amylase and lipase activities in the sera of patients taking 2′,3′ dideoxyinosine (ddI) may indicate subclinical or impending pancreatitis *(54)*.

Two drugs, pentamidine and ddI, that are frequently given to patients with AIDS, have been implicated as the causative agents of pancreatitis. Pancreatitis was noted in patients taking ddI during early trials of the drugs with a reported incidence of 1–2.4%. More recent data, however, indicate a much higher incidence ranging from 4–23.5% *(55)*. Patients with AIDS and a prior history of pancreatitis taking high doses of ddI or on long-term therapy with ddI, and who are severely immunocompromised or with poor clinical status appear to be at increased risk of developing pancreatitis. In addition, those receiving both pentamidine and ddI may be at increased risk owing to a cumulative effect of both drugs.

Metabolic Causes of Acute Pancreatitis

Hypercalcemia

Abnormalities in calcium homeostasis, particularly a prolonged or excessive increase in calcium, have been associated with cell damage in many tissues, including the pancreas. Alterations in the concentration of cytosolic-free or ionized calcium can induce a diverse array of cellular responses, including changes in the exocrine, endocrine, neurocrine, and paracrine secretions, as well as alterations in cell growth, cell differentiation, and cell death *(56)*. Other effects of prolonged increases in calcium include the activation of calcium-dependent proteases, phospholipases, and endonucleases, the depletion of high-energy phosphate stores, such as adenosine triphosphate (ATP) owing to the collapse of mitochondrial membrane potentials, and cytoskeletal disruption *(57)*. These effects may account for abnormalities in the acinar cells of the pancreas that occur early in the course of acute pancreatitis.

Studies on the pathophysiology of acute pancreatitis indicate that the crucial early events occur within the acinar cells. Initiating events that result in an abnormal sustained increase of acinar cytosolic calcium may precipitate pancreatitis *(56)*. Initiating factors, such as ethanol abuse, hyperlipidemia, and ductal hypertension, may induce pancreatitis through the common mechanism of raising acinar calcium concentrations.

Ethanol may have direct and indirect effects on acinar cell calcium homeostasis. Direct effects include a decrease in pancreatic muscarinic receptors that may lead to an increase in cholinergic tone and increased susceptibility to excessive cholinergic stimulation of acinar cells *(58)*. Indirect effects of ethanol causing abnormalities in acinar cell calcium concentrations may involve acetaldehyde, the primary metabolite of ethanol. Increased concentrations of acetaldehyde may give rise to the production of oxygen-derived free radicals *(59)*, which may cause peroxidation of membrane lipids with resultant disruption in intracellular calcium homeostasis.

Hyperlipidemia may induce sustained increases in acinar cell calcium concentrations precipitating pancreatitis. Low-density and high-density lipoprotein fractions have been shown to increase calcium concentrations in a variety of cell types.

Obstruction of the pancreatic duct by a gallstone, neoplastic mass, or parasite is a known cause of acute pancreatitis. Some studies suggest that calcium may also play a key role in the induction of pancreatitis in these patients. Ductal hypertension results in increased pressure within the acinar lumen and may impair passage of zymogenes from acinar cells as well as impede acinar cell calcium extrusion. In addition, disruption of the acinar cell plasma membrane may interfere further with calcium homeostasis. Direct support for the role of increased acinar cell calcium concentrations in the pathogenesis of acute pancreatitis in patients with ductal abnormalities comes from the finding that verapamil, a calcium channel blocker, has been shown to ameliorate the course of the disease *(60)*.

Finally, a number of drugs and toxins associated with the development of acute pancreatitis may exert their effects through the increase in acinar cell cytosolic calcium concentrations. For example, organophosphorus insecticides and certain anesthetics can cause an increase in acetylcholine released from autonomic nerve synapses. This accumulation of acetylcholine can lead to stimulation of acinar cells and prolonged

increases in acinar cell calcium concentrations. Thiazides may induce pancreatitis owing to their effects at increasing calcium uptake by cells.

Hypertriglyceridemia

Hypertriglyceridemia is a well-recognized cause of pancreatitis; however, the clinical syndrome is not well characterized and the clinical course is ill-defined. Ethanol is thought to play a role in hyperlipidemia. However, it is not certain whether hyperlipidemia results from, or precedes, pancreatitis. Hypertriglyceridemia may result because of a genetic defect in the uptake and metabolism of chylomicrons by cells, or it may be secondary owing to ethanol abuse, diabetes, hypothyroidism, nephrotic syndrome, or use of certain drugs, such as thiazides, estrogen, glucocorticoids, retinoids, and cimetidine.

The frequency of hyperlipidemia in patients with pancreatitis has been reported as ranging from 3–38% *(61)*. There does not appear to be any difference in the course of illness or complications seen in patients with pancreatitis attributed to hyperlipidemia compared with pancreatitis owing to other pathogenesis *(62)*. Acute pancreatitis secondary to hypertriglyceridemia is most often encountered in poorly controlled, obese diabetics. Alcoholics with hypertriglyceridemia are the second most common type of patients presenting with this disorder, whereas nondiabetic, nonalcoholic, nonobese patients with drug- or diet-induced hypertriglyceridemia represent the remaining 15–20% of patients with pancreatitis associated with hypertriglyceridemia *(62)*.

Triglyceride concentrations of <5000 mg/L are rarely, if ever, encountered in patients with hyperlipidemic pancreatitis. Generally, admission triglyceride concentrations in these patients exceed 10,000 mg/L *(62)*. Hyperlipidemic pancreatitis can occur in any age group and has been documented in children with hypertriglyceridemia owing to inborn defects in the lipoprotein lipase system *(63)*.

The mechanism by which hypertriglyceridemia causes pancreatitis is thought to be chemical irritation of pancreatic acinar cells or capillary endothelium by cytotoxic free fatty acids and lysolecithin released by the action of pancreatic lipase or lipoprotein lipase *(64)*. Studies in animals have shown that the addition of free fatty acids to the perfusate of a canine isolated pancreas preparation produced edema and hemorrhage. Some investigators have also found that the pancreas preferentially utilizes lipids as metabolic substrate *(62)*. This preference for fatty acids may explain why the pancreas is rich in lipolytic enzymes and why hyperlipidemia may predispose the pancreas to injury.

Postoperative Pancreatitis

Postoperative pancreatitis has been described as a consequence of gastric surgery, biliary tract surgery, renal and liver transplantation, and cardiovascular surgery *(65,66)*. Postoperative pancreatitis also occurs following surgery not involving the abdomen. Patients suffering postoperative pancreatitis usually experience more frequent complications and higher mortality than patients experiencing pancreatitis owing to other pathogenesis. Complications of postoperative pancreatitis, such as pseudocyst, are more common. The higher mortality rate may be the result of the diagnosis being missed more frequently in this patient population as well as other concomitant disease processes being present. Postoperative pancreatitis may be difficult to recognize, particularly following procedures involving the abdomen, because

incisional pain may mask pancreatic abdominal pain, the use of analgesics may blunt the abdominal pain, and because ileus is a common finding in patients undergoing abdominal surgery. The incidence of postoperative pancreatitis has been difficult to establish. In patients who are studied at autopsy, it is often difficult to establish whether the patient died of acute pancreatitis or whether acute pancreatitis was a consequence of the terminating event *(65)*.

Factors claimed to be responsible for causing postoperative pancreatitis are numerous, although the exact mechanisms are uncertain. Direct pancreatic injury as a consequence of abdominal surgery has long been the obvious candidate. However, pancreatitis occurring as a result of extra-abdominal surgery suggests that some other mechanism(s) must also be responsible. Pancreatic ischemia has been frequently suggested as a cause of postoperative pancreatitis, especially in patients placed on cardiopulmonary bypass. In these individuals, pancreatic injury may be mediated by oxygen-derived free radicals *(67)*. Production of these free radicals may be caused by the conversion of the enzyme xanthine dehydrogenase to xanthine oxidase. Previous studies have shown that inhibition of xanthine oxidase can provide some degree of protection to the ischemic pancreas *(67)*. In addition to ischemia as a cause for activation of xanthine oxidase, endogenous pancreatic enzymes, such as chymotrypsin, are potent catalysts of the proteolytic conversion of xanthine dehydrogenase to the oxidase form. Thus, the pancreas may be especially susceptible to injury from free radicals owing to its ability to convert xanthine dehydrogenase to xanthine oxidase via proteolytic cleavage.

Other mechanisms suggested as initiating postoperative pancreatitis include the use of perioperative medications, especially calcium replacement therapy *(68)*. Also, the production of microthrombi with resultant pancreatic ischemia, especially in patients undergoing cardiac valve replacement therapy, has been suggested as another mechanism of postoperative pancreatitis *(66)*. Other postulated factors include obstruction of the pancreatic duct and infections. In patients undergoing organ transplantation, the use of immunosuppressive, drugs such as azathioprine and corticosteroids, may be responsible for initiating pancreatitis.

Pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP) is a serious problem that often requires prolonged hospitalization and surgical intervention. In addition to acute pancreatitis, other complications of ERCP include infection of a pre-existing pseudocyst, sepsis related to cholangitis, and injury from the instrument itself. The incidence of pancreatitis following ERCP has been reported as 1–5%, although the incidence of hyperamylasemia has been reported to be as high as 70% *(69,70)*. There is conflicting evidence concerning the severity of post-ERCP pancreatitis. Most reports suggest that pancreatitis following this procedure is relatively mild with few complications and infrequent mortality. However, in one series, 50% of patients who developed pancreatitis following ERCP required prolonged hospitalization, aggressive nutritional support, or surgical therapy *(69)*. Mortality in these same patients was 13%. Several factors have been implicated in the pathogenesis of post-ERCP pancreatitis. The type and ionic strength of contrast material used, the volume of contrast material injected, and repeated injections of the pancreatic duct have all been cited as factors. Successful treatment of ERCP-induced pancreatitis requires early recognition and institution of appropriate therapy. Further investigations into the

exact mechanisms by which ERCP induces pancreatitis are needed so that complications can be prevented.

Ethanol

The association between ethanol consumption and acute pancreatitis is well documented, and has been known for over 100 yr. Alcohol usually accounts for the greatest number of episodes of pancreatitis in males, whereas females tend to have pancreatitis more often from biliary obstruction. Ethanol-induced pancreatitis can develop following binge drinking; however, it usually develops in patients following chronic ingestion of large quantities of alcohol over a prolonged period, usually at least 7–10 yr *(71)*.

Many theories for the pathogenesis of alcohol-induced pancreatitis have been proposed. Mechanisms include alcohol-induced stenosis of the sphincter of Oddi resulting in pancreatic hypersecretion, biliary pancreatic reflux, duodenal-pancreatic reflux, and alcohol-induced reduction of pancreatic blood flow *(71)*. Another mechanism recently proposed suggests that toxic metabolites of ethanol are involved in the generation of free radial species, which are responsible for pancreatic injury. Both the superoxide radical and hydroxyl radical appear to be important early mediators of this injury.

The primary metabolite of ethanol oxidation is acetaldehyde. Acetaldehyde is an excellent substrate for the enzyme xanthine oxidase. Xanthine oxidase is present in normal tissue primarily as the dehydrogenase form, termed xanthine dehydrogenase. Xanthine dehydrogenase must be converted to the oxidase form prior to metabolism of acetaldehyde. This conversion can be readily achieved in the pancreas by the action of proteolytic enzymes released from the inflamed pancreas. A period of pancreatic ischemia is also required before acetaldehyde induces the injury seen in pancreatitis. The ischemia is necessary for the conversion of xanthine dehydrogenase to xanthine oxidase *(72)*. Free radicals are generated when acetaldehyde is oxidized by xanthine oxidase. The administration of compounds, such as superoxidase dismutase and catalase, scavengers of free radicals, and allopurinol, an inhibitor of xanthine oxidase, have been found to minimize this injury. These findings lend further support for the role of toxic oxygen metabolites in the pathogenesis of ethanol-induced pancreatitis.

Another mechanism whereby alcohol may induce pancreatitis is through a reduction in pancreatic blood flow. Pancreatitis has been observed in association with low blood flow rates. Studies of the effect of alcohol on pancreatic perfusion have also demonstrated that high doses of ethanol can reduce pancreatic blood flow without altering systemic circulatory parameters *(73)*. Alcohol administration is associated with decreased pancreatic hemoglobin oxygen saturation, despite stable hemoglobin content and systemic cardiorespiratory parameters. These findings may be owing to a state of pancreatic ischemia produced by a reduction in capillary blood flow *(73)*. The pancreas, in particular, may be more susceptible to ethanol-induced perfusion disturbances compared to other organs. Hemoglobin oxygen saturation has been noted not to be affected in kidney or stomach following ethanol administration.

Other mechanisms have also been suggested by which ethanol may cause pancreatic hypoxia. A reduction in capillary blood flow following ethanol administration may result in edema of the acinar cells with consequent compression of the capillaries *(74)*.

Another mechanism of ethanol-induced pancreatitis may be via aggregation of erythrocytes. Aggregation of erythrocytes has been demonstrated in the bulbar conjunctiva following acute ethanol intoxication *(75)*.

Anatomic Abnormalities

Anatomic abnormalities of the pancreas have been reported to cause acute pancreatitis. The most common anatomic variant of the pancreas is pancreas divisum. This condition results from a failure of the dorsal and ventral pancreatic ducts to fuse during embryological development. Pancreas divisum has been implicated as the source of 10–20% of cases of previously unexplained pancreatitis. However, the debate still continues regarding whether this condition is a cause of acute pancreatitis. Pancreas divisum affects 5–7% of the general population. Some investigators suggest that the development of pancreatitis in patients with pancreas divisum is common *(76)*. The mechanism by which pancreas divisum causes pancreatitis is owing to stenosis.

The dorsal portion of the pancreas drains through the minor papilla, whereas the ventral portion drains through the major papilla. Since the bulk of pancreatic secretions drain via the minor papilla, functional obstruction is created, because the minor papilla is too small for the volume of secretions presented to it. In patients with this condition, surgical enlargement of the accessory ampulla may help to mitigate or prevent further episodes of pancreatitis. It has been suggested that aggressive examination of patients with unexplained or idiopathic pancreatitis may uncover a large percentage of those with pancreas divisum as a cause of the pancreatitis that can be corrected surgically *(77)*.

Other anatomical abnormalities that may result in pancreatitis include dysfunction of the sphincter of Oddi or ampullary stenosis. The incidence of this problem is unknown. However, these conditions may be responsible for some cases of unexplained pancreatitis.

Infection

A variety of infectious agents have been associated with the development of acute pancreatitis. Viral, bacterial, and parasite causes have been documented. Viral infections associated with the development of acute pancreatitis include mumps, rubella, Coxsackie B, Epstein-Barr virus, cytomegalovirus, hepatitis A, B, non-A and non-B.

Opportunistic infections affecting the pancreas in individuals who are immunocompromised because of infection with HIV create a substantially increased risk for the development of pancreatitis. It is thought that up to two-thirds of cases of pancreatitis in patients with HIV are owing to infection. Agents implicated in causing pancreatitis in these patients include cytomegalovirus, cryptococcus, *Toxoplasma gondii*, Cryptosporidium, *Mycobacterium tuberculosis*, and *Mycobacterium avium* complex *(78)*. The remaining one-third of cases of pancreatitis associated with HIV infection are thought to be induced by some of the drugs that these patients take.

Infestation and obstruction of the biliary system by parasites can also cause pancreatitis. The most common agent is *Ascaris*.

Biliary Obstruction

The exact frequency of pancreatitis owing to biliary obstruction is unknown. Some reports indicate that the incidence may be high as 60–80%. The true incidence of bil-

iary pancreatitis is most likely a reflection of the type of patient population served by a particular institution. Hospitals that administer to a predominantly male patient population, especially if of a lower socioeconomic status (e.g., Veteran's Administration Hospitals), will probably see a fairly low incidence of biliary pancreatitis; the majority of patients in this group have alcohol-associated pancreatitis. Gallstone pancreatitis is seen more frequently in females.

The association between acute pancreatitis and gallstones is owing to impaction and transient obstruction of the ampulla of Vater by a migrating gallstone *(79)*. However, acute pancreatitis develops in only 4–8% of patients with cholelithiasis *(80)*. Factors that may predispose some patients with gallstones to pancreatitis include the number and size of gallstones in the gallbladder, and the anatomy and motor function of the biliary tract.

The early detection of biliary obstruction in patients with acute pancreatitis is essential because of differences in management of these patients vs patients with acute pancreatitis owing to other pathogenesis. Patients with acute pancreatitis resulting from biliary obstruction may be at greater risk for the evolution of pancreatic edema to hemorrhage and necrosis, because persistent ampullary obstruction has been shown to increase the severity of the attack *(81)*. Although most cases of biliary pancreatitis are self-limiting, severe acute pancreatitis is seen in 20% of these patients, and is associated with increased morbidity and mortality. Although the debate regarding the optimal timing (early vs delayed) of stone removal and the best approach (surgical vs endoscopic) has yet to be settled, patients with acute pancreatitis owing to biliary obstruction often benefit from biliary decompression *(82)*.

Ultrasonography is the test of choice for the detection of cholelithiasis; however, it gives only indirect evidence in support of a biliary pathogenesis of acute pancreatitis. A spectrum of ultrasound findings can be seen in patients with gallstone disease. These findings range from the presence of sludge in the gallbladder, the presence of "sludge balls" composed of mucus and crystals, microcalculi, and stones *(83)*. It has been speculated that up to 75% of patients with pancreatitis for which no cause can be found is owing to the presence of biliary sludge or microcalculi that are not readily discerned on ultrasound examination. However, examination of duodenal fluid for crystals or microcalculi will often show these entities to be present. Several conditions can predispose individuals to supersaturation of bile with resultant formation of crystals and stones. These include prolonged fasting, pregnancy, and individuals on a diet low in calories for purposes of weight loss.

Attempts to discriminate biliary from nonbiliary origins of acute pancreatitis by use of radiologic contrast studies have proven unreliable, especially in the early stages of the disease when accurate diagnosis is essential. Biochemical markers, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and total bilirubin, have also been evaluated in an effort to discriminate biliary from nonbiliary pancreatitis. Some studies have found these markers helpful in discriminating biliary from nonbiliary pancreatitis, whereas others have found them of limited diagnostic utility *(27–29)*.

The ampullary obstruction causes a rapid increase in bile duct pressure with consequent liver cell damage, and release of aspartate aminotransferase and alanine aminotransferase. Increases in alkaline phosphatase and bilirubin have also been observed in

patients with biliary pancreatitis. However, significant increases in these may not occur if the bile duct is obstructed only transiently. Passage or removal of gallstones that have been obstructing the biliary tract results in a sudden decrease in biliary pressure and normalization of enzyme activities. The rapidity and transient nature of enzyme changes in patients with pancreatitis owing to biliary obstruction make it essential that frequent serial determinations be performed.

ASSESSMENT OF THE SEVERITY OF ACUTE PANCREATITIS

Assessment of the severity of acute pancreatitis plays an important role in the treatment plan. Severe cases of acute pancreatitis can often be cured by medical treatment if the disease is restricted to interstitial inflammation. However, if pancreatic necrosis develops, the patient has a high risk of local infection and generalized sepsis that can lead to multiple system organ failure. In patients who develop pancreatic necrosis, prompt surgical removal of necrotic tissue can significantly improve patient outcome. Patients with pancreatic necrosis who have surgery delayed past the onset of systemic complications have significantly higher postoperative mortality compared to those patients who are quickly identified as requiring surgery. Thus, it is important that patients with evolving pancreatic necrosis be quickly identified so that appropriate treatment may be given.

Approximately 85–90% of attacks of acute pancreatitis are self-limiting and pass without significant morbidity within 3–7 d. The remaining 10–15% of attacks are more severe and are associated with a 50% mortality *(84)*. The ability to predict disease severity accurately and to monitor the course of an attack is advantageous for a number of reasons including:

1. To ensure that intensive therapy is targeted at patients with severe attacks and to evaluate the efficacy of such therapy;
2. To allow for the early detection of complications;
3. To satisfy requirement for entry of patients into therapeutic trials; and
4. To facilitate the comparison of disease severity of patients that present to different institutions *(85)*.

The system used for the prediction of disease severity should be sufficiently sensitive so that intensive therapy is not withheld inappropriately.

The most severe episodes of acute pancreatitis and those associated with the highest mortality are the first and second attacks of acute pancreatitis. However, an exception to this rule is pancreatitis associated with hyperlipidemia. In these cases, any episode may be severe with a fatal outcome *(86)*. Pancreatitis that occurs as a result of ethanol abuse is associated with lower mortality when compared with pancreatitis owing to other causes.

Many schemes have been developed for use as predictors of disease severity. The types of predictors may be based on one or more combination of the following: clinician's assessment, multiple prognostic criteria, results of the peritoneal tap, computerized scanning, and use of biochemical test results *(87)*. In addition, the definition of severity itself may differ. For example, some studies define severe disease as the presence of hemorrhagic or necrotizing pancreatitis, whereas others define disease severity in terms of complications, mortality, or spending more than a predetermined number of days (e.g., 7) in an intensive care unit.

Prediction of severity based on clinical assessment is often inaccurate, especially when performed early in the course of the disease. Initial clinical assessment can predict approx 40% of those who will develop severe disease. However, when performed within 24 h following admission, clinical assessment can predict up to 75% of patients likely to develop severe disease *(88)*. Thus, some mechanism for identifying patients early in the course of the disease would be of great benefit. A clinical assessment in terms of sensitivity and specificity has shown that the clinician's assessment has poor sensitivity, but excellent specificity for predicting disease severity *(87)*.

The use of multiple prognostic criteria for establishing disease severity has gained wide acceptance since being established by Ranson in 1974 *(89)*. This classification scheme was based on the findings of 11 clinical and biochemical factors. Five of these factors were determined on admission, and the other six were determined during the ensuing 48 h. Mortality was found to be <1% if two or fewer risk factors were present, 40% if five or six risk factors were found, and essentially 100% if seven or more signs were present. This scoring system has been found to classify approx 90% of patients accurately with respect to disease severity. The original list proposed by Ranson has since been modified by others. The Glasgow score first proposed in 1978 utilized nine of the original criteria proposed by Ranson, although with some modifications to the cutoff values *(90)*. A re-evaluation of the Glasgow score in 1984 revealed that the diagnostic accuracy of the scoring system could be improved if aspartate aminotransferase (AST) was removed as one of the predictive factors.

In addition to the scoring systems developed by Ranson and the Glasgow score, other severity scores have been developed. The original Acute Physiology and Chronic Health Enquiry score (APACHE) is based on 34 physiologic variables, the sum of which yields a score *(91)*. The underlying utility of the APACHE score is that the severity of acute disease can be assessed by quantifying the degree of abnormality of multiple physiologic variables. The APACHE II classification system is a revised version of the original APACHE scheme; however, only 14 clinical and biological parameters are used, instead of the original 34. An advantage of the APACHE II score over the Ranson or Glasgow scores is that the former can be evaluated immediately on admission and throughout the whole hospital stay; this allows for a more rapid prognostic classification of the patient.

A variety of other scoring systems have also been developed. The Simplified Acute Physiology Score (SAPS) is derived from the APACHE score. Evaluation studies comparing these different systems have demonstrated that the APACHE II score is superior to the other prognostic classification schemes *(85)*. Reasons given for its superior performance include the use of all the major risk factors that influence outcome from disease and the semiquantitative use of varying weights assigned to increasingly abnormal values instead of a qualitative "yes" or "no" answer. The use of a semiquantitative weighting scheme provides for a greater range of values between mild and severe attacks. Unfortunately, however, none of the scoring systems is particularly good at predicting late complications; in addition, the prediction of a pancreatic pseudocyst is poor *(92)*.

A simplified approach for classification of patients with respect to disease severity is the use of single prognostic indicators. Whereas the APACHE and Ranson scores rely on a multitude of biochemical and clinical indicators, the use of a single, rela-

tively inexpensive, rapid, and reliable blood or urine test to replace the cumbersome multiple criteria scores would be advantageous *(93)*.

A variety of enzyme and other protein markers have been proposed for gauging severity in acute pancreatitis. Although increases in amylase and lipase are the hallmarks of pancreatitis, increases in a multitude of other enzymes are observed, some of which have been proposed as prognostic indicators. It is unfortunate that although amylase and lipase are universally used for the diagnosis of pancreatitis, the magnitude of increase in either enzyme has no prognostic value. One study of 417 patients with acute pancreatitis found that the mortality rate was greater in patients with amylase activities <1000 U/L compared to those with amylase activities much >1000 U/L *(94)*. However, the P_3 isoamylase fraction has been found to be of prognostic significance *(95)*. In one study, approx 90% of patients with an unfavorable outcome had an increase in the P_3 isoamylase at the time of discharge *(96)*. Thus, careful follow-up of patients with increased P_3 isoamylase at the time of discharge may be appropriate.

Neutrophil Elastase

Data suggest that excessive activation and release of endogenous humoral mediators from polymorphonuclear neutrophils, monocytes, and macrophages may be responsible for the severity of complications in acute pancreatitis. The activation of neutrophils and monocytes at sites of inflammation results in the release of biologically active products. The products include proteolytic enzymes, such as elastase, reactive oxygen species, and cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor. Elastase is a serine protease that can degrade elastin, collagen, clotting factors, immunoglobulins, protease inhibitors, and transport proteins, such as ferritin. Normally, individuals are well protected against the effect of proteolytic enzymes, because 60% of plasma proteins function as protease inhibitors *(97)*. The effects of elastase include increased pulmonary vascular resistance, decreased cardiac output, pulmonary leukostasis, and disseminated intravascular coagulation *(98)*. Elastase concentrations in plasma have been shown to correlate directly with severity of acute respiratory distress syndrome, sepsis, and multiple organ failure *(99,100)*.

Numerous studies have demonstrated good prognostic accuracy for patients with acute pancreatitis using neutrophil elastase *(101–103)*. The time-course of this test reveals that maximal concentrations are attained 24–48 h following disease onset, and increased concentrations are associated with worsening prognosis. Although test procedures are available commercially, measurement of elastase is not performed routinely in most clinical laboratories. In addition, leukocytes contain high concentrations of the enzyme. The latter requires the careful and prompt separation of plasma from the specimen following blood collection.

Acute-Phase Proteins

The acute phase of pancreatitis is characterized by certain predictable changes in the production of pancreatic proteins and other markers of inflammation and injury. Whereas the expression and production of many pancreatic enzymes and other proteins decrease following the onset of acute pancreatitis, the production of certain stimuli, including cytokines and tumor necrosis factor, is enhanced. These agents are

produced from the damaged tissue and from activated mononuclear cells. Cytokines elicit the biological effects that are characteristic of the acute phase response.

The proteins that are characteristic of the acute-phase response are divided into one of two classes based on their pattern of regulation by cytokines *(104)*. Synthesis of class 1 acute-phase proteins, including C-reactive protein (CRP), haptoglobin, and α-1-acid glycoprotein, is induced by IL-1 or a combination of IL-1 and IL-6. The class 2 acute-phase proteins, such as α-2-macroglobulins, α-1-antichymotrypsin, pancreatitis-associated protein (PAP), and fibrinogen, are regulated primarily by IL-6 and glucocorticoids *(105)*.

C-Reactive Protein

Increased concentrations of CRP in patients with acute pancreatitis are owing to activation of the monocyte-macrophage system *(106)*. Concentrations >150 mg/L have been shown to be highly suggestive of severe acute pancreatitis *(107)*. Maximal CRP concentrations generally are reached 2–4 d following the onset of disease. The prolonged time-course of CRP is thus of limited clinical utility. At 48 h postonset, CRP was no better at predicting severity than a multiple criteria scoring system *(107)*. The use of CRP as a prognostic indicator also suffers from the nonspecificity of this test for pancreatic disease. Individuals with any other type of acute inflammatory process may show increased CRP concentrations. However, even the limitations of CRP should not preclude its use; the analyte is readily available in most laboratories, is easy to perform, and is relatively inexpensive.

Trypsinogen Activation Peptide (TAP)

A new marker of disease severity that has not been extensively evaluated is urinary concentrations of TAP. The use of TAP to predict severity is based on the concept that mild pancreatitis occurs in patients without activation of trypsinogen to trypsin. If the amount of activated trypsin exceeds the availability of antiproteases to inhibit trypsin activity, then release of active trypsin into the systemic circulation occurs with its adverse effects. Thus, the amount of active trypsin with concomitant production of TAP is directly related to disease severity.

TAP is a five amino acid compound that is released from trypsin following activation. Although free trypsin is normally rapidly complexed to antiprotease inhibitors, TAP is not. Since TAP has a low molecular weight and is unbound in serum, it is rapidly excreted into urine following its formation. One study that evaluated urinary TAP, serum CRP, and the Glasgow criteria for discriminating mild from severe acute pancreatitis found TAP the best indicator of disease severity on admission and at 24 h following admission *(108)*.

Pancreatitis-Associated Protein (PAP)

Another relatively new marker of disease severity is PAP. This protein is barely detectable in normal pancreatic tissue; however, following the onset of acute pancreatic damage, the enzyme is synthesized in the acinar cells of the pancreas. The increased synthesis of PAP by the acinar cells following pancreatic injury is unique; the synthesis of pancreatic enzymes is normally repressed during the acute phase of an attack *(109)*. This finding may partially explain why serum pancreatic enzyme

activities quickly decline following their initial rise and why severe attacks of acute pancreatitis are often associated with lower enzyme activities when compared with mild attacks *(110)*.

PAP is a secretory protein and leaks into the bloodstream following its synthesis. PAP may offer some advantages when compared to other protein markers, such as TAP and CRP. PAP is expressed in response to pancreatic damage, whereas TAP is produced from trypsinogen whose synthesis is repressed during acute pancreatitis. PAP might also offer better specificity for pancreatic damage when compared to CRP, because the latter is not synthesized by the pancreas.

In addition to acute pancreatitis as a cause of increased serum PAP concentrations, long-term chronic use of ethanol has been found to lead to approx 10-fold increases in serum PAP *(111)*. The highest concentrations have been observed 2 d following cessation of ethanol use. These patients did not develop other signs of symptoms suggestive of acute pancreatitis, and the results further support the suggestion that heavy long-term consumption of ethanol induces subclinical pancreatic damage, but not clinical pancreatitis.

Concentrations of PAP obtained following admission have been found not to correlate with the severity of pancreatitis. Apparently, the induction of PAP gene expression starts several hours following the onset of an attack, after which PAP concentrations may increase more than 100 times baseline values within a few days *(112)*. Thus, PAP is most likely a useful test in the follow-up of patients with acute pancreatitis. Monitoring of PAP during the acute phase of an attack may provide information on the development and severity of the disease. An initial rise followed by a persistent decrease in PAP concentrations appears to predict recovery; consistently increased concentrations are associated with poor outcome. Unfortunately, no procedures for measuring PAP are available commercially.

Complement

Activation of complement with release of anaphylatoxins has been demonstrated in patients with acute pancreatitis *(113)*. Activation of the complement system can occur owing to proteases, such as trypsin, or from tissue injury as a result of hypoperfusion, thermal injury, or mechanical trauma. In addition, the complement system can be activated in patients with acute pancreatitis who have intravascular coagulation and fibrinolysis *(114)*.

Anaphylatoxins including $C3_a$ and $C5_a$ are formed from C3 and C5 following the activation of complement. $C3_a$ and $C5_a$ mediate an increase in vascular permeability, induce contractions of smooth muscle, cause release of histamine from mast cells and basophils, and may even impair cardiac function *(97)*. The active anaphylatoxins ($C3_a$ and $C5_a$) are inactivated by an anaphylatoxin-inactivator enzyme. However, even when inactivated, $C5_a$ still retains the ability to stimulate neutrophils.

Activation of the complement system also results in the formation of a terminal–complement complex, and the presence of this complex in plasma indicates that complete activation of complement has occurred. Patients with moderate to severe pancreatitis have higher concentrations of activated and inactivated anaphylatoxin $C3_a$ as well as the terminal complement complex when compared to patients with mild pancreatitis.

Interleukin-6

Experimental studies have shown that IL-6, which is released primarily by activated mononuclear phagocytes, is the principal mediator of the acute-phase protein response of which CRP is an important component *(115)*. Serum concentrations of IL-6 begin to rise during the first 24 h following the onset of an attack of acute pancreatitis and peak between 24 and 36 h. Peak concentrations of CRP occur between 36 and 48 h following the onset of symptoms. Thus, measurement of IL-6 concentrations may allow earlier prediction of disease severity owing to its earlier rise when compared with CRP. One study of 24 patients found that serum IL-6 concentrations obtained on admission could distinguish between mild and severe attacks of acute pancreatitis *(116)*. IL-6 measured at admission provided a diagnostic accuracy of 75% compared with an admission diagnostic accuracy for CRP of 54%. When peak IL-6 and CRP concentrations were used to gauge disease severity, both markers provided a diagnostic accuracy of 83%.

Measurement of IL-6 may be performed using a bioassay procedure or by use of immunoassay-based methods that are available commercially. The major drawback of the bioassay procedure is its turn around time of 5 d; the immunoassay procedures can provide results within 6 h *(116)*.

Tumor Necrosis Factor

Tumor necrosis factor (TNF) is another multifunctional cytokine that is involved in the acute-phase response to trauma, bacterial infection, and inflammation *(117)*. TNF is a potent inducer of secretion of IL-6 from leukocytes and therefore appears in the circulation earlier than IL-6. Once released into the circulation, TNF induces the activation of the enzyme PLA_2 and mediates the release of toxic oxygen-derived metabolites, causing necrotic cell lysis that finally results in hemorrhagic necrosis *(118)*. Increased concentrations have been observed in a variety of conditions, including sepsis, and in patients with multiorgan failure.

The role of TNF in the evaluation of the severity of acute pancreatitis is still not completely defined. One study found that increased TNF concentrations in serum during the first 24 h of an attack were helpful in predicting complicated and fatal pancreatitis *(119)*. However, later studies have not corroborated these findings *(117)*. Possible explanations for these differences may be owing to the rapid time-course in which TNF rises and falls in serum. In those patients with septic shock where TNF concentrations may reach extraordinary values, the increase occurs for a few hours only *(120)*. Since circulating TNF has a half-life of only 5–25 min, those studies that evaluated TNF as a marker of disease severity, and collected only one sample or collected one sample every few days could have easily missed the rapid rise and fall of TNF *(117,120)*. It appears that appropriate use of TNF as a marker of disease severity requires frequent serial sampling. The utility of TNF as a marker of disease severity has not yet been adequately addressed, and further studies are needed to define its role.

Ribonuclease

Increased activity of ribonuclease in serum has been reported in a variety of conditions, including acute necrotizing pancreatis, pancreatic cancer, and other neoplas-

tic diseases *(121)*. Ribonuclease is useful for the discrimination of patients with acute interstitial pancreatitis from those with acute necrotizing pancreatitis; the latter have increased ribonuclease activities *(121)*. An earlier study found that only one of 25 patients with normal ribonuclease activities developed evidence of pancreatic necrosis, whereas 11 of 13 patients with increased ribonuclease developed a pancreatic abscess or necrosis *(122)*.

The utility of ribonuclease for the identification of patients with severe acute pancreatitis is limited by several factors. Most notable is the effect of impaired renal function on serum ribonuclease. Increasing serum ribonuclease values correlate directly with increasing serum creatinine concentrations. Ribonucleases are low-mol-wt proteins that are eliminated predominantly by the kidneys. Thus, ribonuclease may be a useful marker for severe cases of pancreatitis in the absence of renal insufficiency. Unfortunately, renal insufficiency is a common finding in patients with acute necrotizing pancreatitis. Another factor that hampers evaluation of the clinical utility of this test is the fact that several different isoenzymes of ribonuclease are present in serum, each possessing its pH optimum and substrate specificity. Thus, it is often difficult to compare results obtained by different investigators owing to differences in the methods used to measure ribonuclease activity. A third factor that can interfere with ribonuclease measurements is the effects of hemolysis. Erythrocytes have been found to contain inhibitors of ribonuclease activity and can therefore lead to falsely decreased measurements of ribonuclease activity.

Antiproteases

Following the onset of an attack of acute pancreatitis, high concentrations of pancreatic secretory enzymes are released into the circulation. The finding that protease activity is usually absent following the onset of acute pancreatitis is because active proteases are scavenged by protease inhibitors present in the circulation. Evidence that active proteases are released into the circulation is provided by the finding that antiproteases, such as α-2-macroglobulin, are decreased in patients with acute pancreatitis. It is one of two primary protease inhibitors that preferentially bind activated proteolytic enzymes, including trypsin, chymotrypsin, and elastase. In patients with acute pancreatitis, α-2-macroglobulin concentrations decrease in proportion to the severity of the attack *(123)*. Binding of proteases by α-2-macroglobulin results in the formation of a complex that is cleared from the circulation by the reticuloendothelial system. The protease–antiprotease complex has a half-life of approx 10 min compared with several hours for the uncomplexed form.

The trypsin binding capacity of α-2-macroglobulin has been reported to decrease to 70–80% of normal following an attack of acute pancreatitis *(124)*. The lowest concentrations usually occur 3–9 d following the onset of an attack.

Another important protease inhibitor present in serum is α-1-antiprotease. In human serum, 90% of trypsin inhibitory capacity is attributable to α-1-antiprotease with α-2-macroglobulin accounting for much of the remainder. α-1-antiprotease is an acute-phase reactant. Concentrations of this protein begin to rise soon after the onset of symptoms of an attack of acute pancreatitis and peak between 3 and 7 d. The most severe attacks of acute pancreatitis are often associated with the greatest increase in α-1-antiprotease *(125)*.

Not all studies have been able to demonstrate good diagnostic utility of antiproteases for discriminating mild from severe attacks of acute pancreatitis *(107,126)*. Reported positive and negative predictive values for α-2-macroglobulin and α-1-anti-trypsin measured during the first 48 h of an attack were 82 and 67%, and 59% and 50%, respectively *(127)*. Another study found that LD had a diagnostic accuracy of 82% compared with diagnostic accuracies of just 71 and 69% for α-2-macroglobulins and α-1-antitrypsin, respectively *(126)*.

Phospholipase A (PLA)

Measurement of PLA has been advocated as a test for the severity of acute pancreatitis; greatly increased activities of PLA are associated with severe hemorrhagic forms of the disease, and lesser increases are found in the mild edematous type *(128,129)*. PLA that reaches the circulation is converted from its proenzyme form to active PLA by trypsin. No inhibitors are present in serum to mediate the action of active PLA, and it is thought to play an important role in the cause of pulmonary insufficiency often associated with acute pancreatitis. The enzyme has been found to destroy lecithin found in pulmonary surfactant as well as in cell membranes.

Although many studies have found an association between PLA activity and severity of disease *(128–130)*, one has not *(131)*. Increased PLA activities are found in a wide variety of conditions not involving the pancreas, including liver disease, renal failure, trauma, surgery, and cardiac disease *(131)*. Thus, although PLA may contribute to the organ necrosis and mortality of patients with acute pancreatitis, increased PLA is not specific for dysfunction of any one organ system or for any clinical syndrome. Substantial quantities of PLA have been found in leukocytes *(132)*. Release of PLA into the circulation following the activation of these cells may explain the increased PLA activities seen in patients with nonpancreatic inflammatory disorders.

Measurement of PLA in serum may be performed by the quantitation of active enzyme present or by measurement of immunoreactive PLA concentrations. Controversy still exists regarding what method, enzymatic vs immunologic, should be used for measurement of PLA *(133)*. One study showed that enzymatic, but not immunologic PLA measurements provided good positive and negative predictive value of 71 and 82%, respectively, for detecting pancreatic necrosis *(134)*. However, other studies have indicated that immunoreactive PLA is a more sensitive marker than enzymatic PLA for detecting severe cases of acute pancreatitis *(135)*.

Body Mass Index

One easily obtained parameter that may provide prognostic information is the body mass index. One study has shown that patients with a body mass index of >30 kg/m^2, as derived from the patient's height and weight, had poorer outcomes following acute pancreatitis more frequently than patients who were not significantly overweight *(136)*.

Methemalbumin

The recognition of a brown pigment in the serum of patients with hemorrhagic pancreatitis was noted by Edmondson in 1952 *(137)*. The pigment was later characterized as methemalbumin, and its use as a marker of hemorrhagic pancreatitis was

further characterized *(138)*. Methemalbumin is produced via the oxidation of heme that is initially produced from the breakdown of retroperitoneal hemoglobin into heme by pancreatic enzymes. Heme is oxidized to hematin, which is absorbed into the systemic circulation were it combines with albumin to form methemalbumin. Methemalbumin concentrations increase within the first 24 h following the onset of an attack and remain increased for several days.

Studies that have used methemalbumin as an indicator of disease severity have produced variable results *(139,140)*. When used as a predictor of death and complications, methemalbumin has been found to be relatively insensitive *(140)*; however, if methemalbumin is used as a predictor of mortality only, then test sensitivity increases substantially with the predictive value of an abnormal test result often exceeding 90% *(87)*. Thus, methemalbumin measurements appear to be most useful as an indicator of the severest types of acute pancreatitis. When used in this way, methemalbumin is more useful than the criteria of Ranson for predicting fatal attacks of acute pancreatitis *(139)*.

Peritoneal Tap

Similar to methemalbumin in its ability to predict the severest cases of acute pancreatitis is the peritoneal tap. The peritoneal tap may also be used to differentiate an acute surgical abdomen from acute pancreatitis. Aspiration of dark, nonodorous, prune juice-colored fluid is characteristic of severe necrotizing pancreatitis, whereas fluid obtained from the patient with a perforated viscus is usually foul-smelling and contains bacteria *(141)*. A study of 79 patients using peritoneal lavage found that the severest attacks of acute pancreatitis could be expected when one of the following was present:

1. Aspiration of more than 10 mL of fluid irrespective of color;
2. Free fluid of dark color; and
3. A straw- or darker colored lavage return fluid *(140)*.

The presence of pancreatic enzymes in lavage fluid has also been investigated as a means for predicting disease severity. Using a scoring system based on the relative activities of amylase and lipase in peritoneal fluid to their respective serum activities, Robert et al. *(142)* found that the presence of both amylase and lipase in peritoneal fluid having activities greater than those seen in serum could identify patients most likely to have a fatal outcome. The mortality rate for the patients studied was just 5% when none or only one enzyme was higher in peritoneal fluid than in serum. However, when both amylase and lipase were present in greater activities in peritoneal fluid compared with their serum activities, the mortality rate was 29%. The major disadvantage of the peritoneal tap is the invasive nature of the procedure. Complications, such as viscus puncture, are unusual with a reported incidence of <1% *(141)*.

COMPLICATIONS OF ACUTE PANCREATITIS

The pancreas is capable of releasing a great quantity of potent vasoactive peptides, hormones, and enzymes following an insult, such as acute pancreatitis. The wide array of biochemical mediators can induce a variety of derangements both locally and systemic. The various prognostic criteria that are employed to gauge disease severity are

early indicators of potential metabolic derangements. Although hypocalcemia, hyperglycemia, and hypertriglyceridemia are usually considered to be the common metabolic complications, acute pancreatitis may also cause a diverse array of derangements that can, in the severest cases, result in multiple organ system failure and death.

Local Complications

Hemorrhage

A variety of mechanisms can result in hemorrhage in patients with acute pancreatitis. Gastrointestinal hemorrhage occurring in association with pancreatic inflammation has been reported with an incidence ranging from approx 1–40%. The cause of hemorrhage may be the result of several mechanisms, including coexistent peptic ulcer disease, stress gastritis, pre-existent esophageal varices, or erosion of a major blood vessel secondary to a pancreatic pseudocyst, necrosis, or abscess. Elastase and other pancreatic enzymes that are released by recurrent or persistent pancreatic inflammation can weaken and erode the wall of the peripancreatic vasculature leading to hemorrhage.

Hemorrhage into the gastrointestinal tract may also be caused by a pancreatic pseudocyst; hemorrhage into a pseudocyst is a relatively frequent and catastrophic event. This mechanism also involves erosion and weakening of peripancreatic vasculature following enzymatic attack. A blood vessel in close proximity to the wall of a pseudocyst may rupture into the pseudocyst. If a communication exists between the pseudocyst and the pancreatic duct, then blood and fluid present in the pseudocyst will be discharged into the duodenum.

Pseudocyst

Pancreatic pseudocysts consist of a fibrous capsule containing necrotic tissue, blood, and secretions. The fluid within the pseudocyst is often rich in proteolytic enzymes. Pseudocysts are commonly associated with chronic pancreatitis, and they may develop in up to 50% of patients with severe, acute inflammation *(143)*. Clinical symptoms of a pancreatic pseudocysts are similar to those accompanying acute pancreatitis, and include abdominal pain, fever, vomiting, and occasionally mild jaundice.

Pseudocysts may form in a variety of locations. They can be found within the pancreas, posterior to the pancreas, in the pararenal spaces, or in the mediastinum. The walls of the pseudocyst are composed of whatever tissue structures first limit its spread. Encapsulation of the pseudocyst occurs owing to evoked inflammatory reactions with the eventual formation of a fibrous wall. This maturation process generally takes from 4–6 wk for the capsule to thicken sufficiently to hold sutures *(143)*. Further growth of a pseudocyst may occur owing to osmotic influx of fluid in response to tissue necrosis within the pseudocyst *(144)*.

Diagnosis of a pancreatic pseudocyst is by use of imaging studies. Approximately 40% of patients with a pseudocyst will have a palpable mass. In 27% of patients, pseudocysts will undergo spontaneous resolution within 3 wk *(145)*; spontaneous resolution after 3 wk is an uncommon occurrence. Pseudocysts are classified as chronic if they remain for longer than 6 wk.

Pseudocysts can cause a variety of potentially lethal complications. Those located at the head of pancreas may cause duodenal obstruction or compress the common bile

duct, resulting in obstructive jaundice. Splenic vein thrombosis may result in splenic infarction or cause hypersplenism owing to congestive splenomegaly. Similarly, thrombosis of the portal vein may cause extrahepatic portal hypertension and esophageal varices. Another important complication of pseudocysts is infection, resulting in an abscess.

Pancreatic Abscess

Pancreatic abscesses occur as a complication in 4% of patients admitted with acute pancreatitis. The incidence of abscess formation increases with the severity of the attack *(144)*. The direct relationship between disease severity and abscess formation probably reflects the amount of tissue necrosis. In patients with a fatal attack of acute pancreatitis, abscesses are found in 50–70% of cases *(146)*.

Because the term "pancreatic abscess" has often been loosely used to describe a variety of infected processes in the region of the pancreas, the term "infected pancreatic necrosis" has been suggested to represent diffuse, infected pancreatic and peripancreatic necrosis, and fluid collections that occur as a complication of acute pancreatitis *(147)*.

Pancreatic abscess can occur as a result of pancreatitis from any etiology. It is more commonly seen in acute rather than chronic pancreatitis, unlike pseudocysts that are more frequently found in patients with chronic pancreatitis.

The diagnosis of pancreatic abscess by use of biochemical indices is not reliable, because standard laboratory studies are generally nonspecific *(148)*. An increase in leukocytes is usually noted, whereas albumin and total calcium concentrations are generally decreased. Serum amylase is increased in fewer than 50% of patients at the time of diagnosis of a pancreatic abscess. In addition, results of liver function studies, including aspartate aminotransferase, alkaline phosphatase, and bilirubin, are within normal limits in the majority of patients with pancreatic abscess. Other laboratory parameters that have been proposed for the evaluation of pancreatic abscess include ribonuclease *(148)*, CRP, α-1-antitrypsin, and α-2-macroglobulin *(149)*. However, none of these tests have good diagnostic accuracy for the detection of pancreatic abscess. At present, computed tomography is the best diagnostic tool for abscess detection; abscess-specific changes are seen in approx 75% of patients *(148)*.

Phlegmon

A pancreatic phlegmon is produced as a result of secondary infection of the pancreas and retroperitoneal tissue in patients with necrotizing pancreatitis. The incidence of phlegmon has been reported to be as high as 18% and may be higher in patients with severe attacks of acute pancreatitis *(144)*. Patients with phlegmon may present with fever, increased amylase and lipase, abdominal pain or tenderness, and leukocytosis. Detection of phlegmon by ultrasound or computed tomography scan is achievable in 30–60% of patients. An abdominal mass is palpable in approx 15% of cases.

BIOCHEMICAL DISTURBANCES ASSOCIATED WITH ACUTE PANCREATITIS

The ability of the pancreas to produce a variety of potent vasoactive peptides, hormones, and enzymes often leads to complications involving other organ systems.

Some of these complications involving the lungs, heart, liver, and kidneys are often not associated with any detectable structural changes occurring in these organ systems. Evidence suggests that biochemical disturbances that occur in patients with acute pancreatitis are primarily responsible for initiating major organ failure.

Hypocalcemia

Hypocalcemia is a frequent finding in patients with acute pancreatitis, reportedly occurring in 30–60% of patients with the disease *(150)*. A strong correlation has been established between patient prognosis and the magnitude of hypocalcemia *(151)*. The exact mechanism for hypocalcemia in acute pancreatitis is still unresolved. Several mechanisms working alone or in conjunction with one another may be responsible.

The sequestration of calcium by saponification of calcium salts in areas of fat necrosis has long been a popular theory for the pathogenesis of hypocalcemia. However, calcium sequestration in areas of fat necrosis has been shown to be insufficient to explain the hypocalcemia seen in these patients. Infusion of calcium into patients with acute pancreatitis and who are hypocalcemic is of little benefit *(152)*. In addition, the amount of calcium sequestered during the process of saponification typically amounts to <2 g, an amount insufficient to cause hypocalcemia owing to the abundant skeletal stores of readily mobilized calcium. Thus, sequestration of calcium in areas of fat necrosis is not considered to be an adequate mechanism accounting for the hypocalcemia seen in patients with acute pancreatitis.

The rapid development of hypoalbuminemia in patients with acute pancreatitis has been suggested to play a predominant role in hypocalcemia. The exact pathogenesis of hypoalbuminia is not certain; possible causes include diminished hepatic synthesis, increased catabolism, urinary loss, or redistribution of albumin within various body compartments. Approximately half of the total amount of calcium in blood is bound to serum proteins with albumin accounting for 80% of the protein-bound calcium. Thus, when the hypocalcemia is corrected by taking into account the serum albumin concentrations, the incidence of "true" hypocalcemia is relatively low. Imrie et al. *(153)* reported that although 68% of their study patients were initially designated as hypocalcemic, the incidence of true hypocalcemia, obtained by correcting serum calcium concentrations for albumin, was only 12%. Measurement of ionized calcium rather than total calcium in serum has been advocated as the best method for assessing calcium status in patients with pancreatitis. However, other investigators have demonstrated decreases in ionized calcium in humans with acute pancreatitis *(154)*, as well as in animals *(155)*, suggesting that hypoalbuminia alone cannot account for hypocalcemia in all patients with acute pancreatitis.

Hypomagnesemia has been implicated in the hypocalcemia of acute pancreatitis owing to the inhibition of both parathyroid hormone (PTH) secretion and its action on calcium mobilization by osteoclasts. The relationship between magnesium concentrations and its role in the hypocalcemia of acute pancreatitis is controversial. Hypomagnesemia is not a consistent finding in patients with acute pancreatitis and magnesium replacement therapy in those patients who are deficient is not always beneficial *(153)*.

The role of hormone imbalances in the pathogenesis of hypocalcemia in acute pancreatitis is controversial. Increased secretion of glucagon may result in hypocalcemia by

directly inhibiting bone resorption or by releasing calcitonin *(156)*. However, not all investigators have found a relationship between these hormones and hypocalcemia *(152)*.

Derangements in the calcium–PTH axis are also often cited as the cause of hypocalcemia in acute pancreatitis. PTH concentrations in patients with acute pancreatitis have been reported as being decreased *(156)*, normal *(157)*, and even increased *(158)*. Decreased PTH concentrations in patients with acute pancreatitis and hypocalcemia have often been attributed to a relative deficiency of PTH owing to failure of the parathyroid glands to maintain secretion of the hormone *(159)*.

An alternative explanation for the decrease in PTH concentrations following acute pancreatitis may be owing to inactivation of PTH by proteolytic enzymes released from the injured pancreas. Brodrick et al. *(160)* reported that the biological activity of bovine PTH, as measured using a chicken kidney plasma membrane adenyl cyclase assay system, is readily degraded by sera from patients with acute pancreatitis. These results suggest that degradation of PTH, as well as other relevant peptides governing calcium homeostasis (e.g., calcitonin), may play an important role in the hypocalcemia of patients with acute pancreatitis.

Hyperlipidemia

Hyperlipidemia in association with acute pancreatitis has been reported in some series to be as high as 50% *(161)*. The hyperlipidemia observed in these patients is usually characterized by abnormally increased triglyceride concentrations of >12,000 mg/L and normal cholesterol concentrations. In some patients, cholesterol concentrations may even be decreased as a consequence of stress.

Some studies have shown a direct relationship between the degree of hypertriglyceridemia and disease severity *(161,162)*. In one study, all patients with triglyceride concentrations greater than approx 18,000 mg/L (20 mmol/L) developed necrotizing pancreatitis *(161)*. In addition, a direct association between hypercholesterolemia and pancreatic necrosis has also been observed. Patients with acute pancreatitis and hyperlipidemia also have a higher likelihood of developing acute respiratory distress syndrome. Embolization of agglutinated lipid particles in lung and other organs, including the kidney, heart, and brain, is another serious concern in these patients.

The issue of whether hypertriglyceridemia is a pre-existing metabolic disorder in these patients, or if it occurs as a consequence of acute pancreatitis is unresolved. Some studies suggest that patients who develop acute pancreatitis have an abnormality in the metabolism of chylomicrons *(163)*. This abnormality causes the pancreatic interstitium to have increased triglyceride concentrations. Lipase present in pancreatic juice results in the production of cytotoxic free fatty acids, which are able to initiate the autodigestive process in the pancreas. In addition, increased serum concentrations of chylomicrons and chylomicron remnants may cause damage to the pancreatic capillaries owing to release of cholesterol crystals during lipolysis that can induce ischemic lesions.

Patients with hyperlipidemia that occurs secondarily to disease states, such as hypothyroidism, diabetes mellitus, pregnancy, and chronic renal failure, are also at increased risk for developing acute pancreatitis. However, the pathogenesis of hyperlipidemia in many patients with acute pancreatitis is not readily explained. The abnormally increased triglycerides in these patients is thought to be secondary

to necrosis of peripancreatic fat *(161)*. Other studies suggest that inhibition of post-heparin lipoprotein lipase and acute deficiency of glucagon may lead to hyperlipidemia in acute pancreatitis *(164)*.

Hyperglycemia

Increased glucose concentrations in serum (>2000 mg/L) have been used as an indicator of poor prognosis. Up to half of patients with acute pancreatitis will develop mild transient hyperglycemia. Another 30% of patients will demonstrate glycosuria, and from 2–10% may develop frank diabetes *(164)*. In addition to hyperglycemia, hypoglycemia has been also noted to occur in <5% of patients *(164)*.

A variety of mechanisms may be responsible for the hyperglycemia in acute pancreatitis. Glucose metabolism is altered in these patients by an increased ratio of glucagon to insulin, resulting in a relative resistance to insulin *(165)*. These patients may also have impaired function of the β-cells and decreased insulin secretion that can further contribute to poor glucose utilization and hyperglycemia. Other hormone imbalances that may contribute to hyperglycemia include increased concentrations of growth hormone, cortisol, and catecholamines.

Individuals with acute pancreatitis exhibit a number of metabolic similarities when compared with patients who are septic. These similarities include an increased expenditure of energy mediated through a hypermetabolic state with increased oxidation of amino acids, increased ureagenesis, and increased gluconeogenesis. These patients also exhibit a net decrease in protein synthesis often leading to malnutrition. Patients with severe, acute pancreatitis often exhibit a hypermetabolic state. The rate of endogenous glucose production has been found to be significantly higher in these patients. However, despite the increase in endogenous glucose production, there is a significant decrease in the percentage of glucose uptake by cells. This imbalance between glucose production and metabolism can also lead to hyperglycemia.

The hypermetabolic state observed in patients with severe, acute pancreatitis is characterized by a fall in systemic vascular resistance and a rise in cardiac output leading to a marked increase in visceral and muscle blood flow and consumption of oxygen. The increase in oxygen consumption and corresponding increased caloric need are met through a variety of mechanisms. The utilization of branched-chain amino acids (isoleucine, leucine, and valine) as substrates for gluconeogenesis and peripheral oxidation is handled through increased catabolism of body protein stores and increased ureagenesis. In addition to increased concentrations of branched-chain amino acids, increased concentrations of aromatic amino acids have also been observed. The excess of amino acids within the circulation can result in the accumulation of aromatic amino acids within the central nervous system and production of false neurotransmitters, such as octopamine and phenylethanolamine.

The extremely high catabolic rates in patients with pancreatitis may result in nitrogen losses as great as 40 g/24 h. Administration of glucose to those patients can serve to inhibit urea production and reduce protein catabolism.

Disseminated Intravascular Coagulation (DIC)

Patients with acute pancreatitis may exhibit coagulation disturbances ranging from scattered intravascular thrombolysis to fatal DIC. Clinically significant DIC is char-

acterized by production of microthrombi and consumption of clotting factors and complement, and is seen occasionally in patients with severe acute pancreatitis. However, subclinical coagulation disorders occur more frequently in these patients; they often exhibit a hypercoagulable state with increased concentrations of fibrinogen and factor VIII. Fibrinogen concentrations peak by d 6 or 7 following onset of the disease. In patients with severe, acute pancreatitis, the occurrence of DIC with associated defibrination, thrombocytopenia, decreased factor VII, and prolongation of the thrombin time has been described frequently *(150)*.

Studies in animals have shown that the concentration of platelets and fibrinogen falls immediately following the onset of acute pancreatitis *(166)*. This initial drop is followed by a subsequent rebound, and in fact, the increased concentrations of fibrinogen and platelets found in patients several days after the onset of acute pancreatitis may represent a rebound from the initial low values occurring shortly after disease onset.

The mechanism for the coagulation disorders seen in patients with acute pancreatitis is not clear. The release of active trypsin into the circulation has been suggested as a cause *(167)*. Induction of DIC in dogs has been accomplished following iv infusion of trypsin *(168)*. Infusion of other pancreatic enzymes, including amylase or lipase, has been found not to induce coagulation disturbances. Other mechanisms postulated to cause this condition include imbalances in the ratio of proteases to antiproteases, an increase in the reactivity of the reticuloendothelial system, and loss of fibrinogen from the circulation owing to vascular injury *(169)*.

The treatment of patients with acute pancreatitis who develop DIC is difficult. To suppress the activation of proteolytic enzymes, the use of enzyme inhibitors, such as aprotinin, has been studied. Unfortunately, the use of aprotinin in patients with acute pancreatitis has been met with limited success *(170)*. The use of nafamostat mesilate may be beneficial to these patients. This synthetic protease inhibitor is able to penetrate the acinar cells of the pancreas readily owing to the low molecular weight of the drug and its strongly amphophilic properties. Studies have shown that nafamostat mesilate is effective for the treatment of both acute pancreatitis and disseminated intravascular coagulation *(171)*.

Systemic Complications of Acute Pancreatitis

During the first week following the onset of acute pancreatitis, severe cases are often complicated by multisystem organ failure. The organ systems most commonly affected include the renal, pulmonary, and cardiovascular systems. Cardiovascular collapse owing to bleeding or myocardial infarction is also possible. A variety of late complications may occur, typically after the second week of illness, such as pseudocyst and abscess formation. A variety of unusual complications, including gastrointestinal hemorrhage, gastric varices, and pancreatic encephalopathy associated with confusion, delusions, and coma, may also occur. Purtscher's angiopathic retinopathy owing to retinal arteriolar obstruction may result in sudden blindness. Pancreatic inflammation may result in obstruction, necrosis, or fistulization of the adjacent colon, whereas the spread of peripancreatic inflammation may result in splenic rupture or hematoma formation *(172)*.

The likelihood of organ failure is closely related to the type of pancreatitis. In patients with edematous pancreatitis, systemic complications develop in fewer than

10%. However, patients with sterile necrotizing pancreatitis develop systemic complications in up to 60% of cases, whereas those with infected pancreatic necrosis almost always exhibit systemic complications *(173)*.

Pulmonary Complications

Clinical evidence of lung injury has been described in up to 70% of patients with acute pancreatitis. Severe lung injury, manifested as acute respiratory distress syndrome or acute respiratory failure, has been reported in approx 15% of patients *(174)*. The exact mechanism for respiratory complications is uncertain. A wide variety of endogenous substances and cellular elements released from necrotic cells have been postulated. Experimental evidence suggests that activated pancreatic proteases, free fatty acids, activated PLA, activated neutrophils, activated complement, and kinins may play an important role *(175)*.

Pulmonary injury found in patients with acute pancreatitis is difficult to distinguish clinically and pathologically from the acute respiratory distress syndrome *(174)*. These pulmonary complications can vary in severity from mild to life-threatening, and may be grouped into various stages depending on the severity of the lesion *(150,164)*.

The first stage that affects the majority of patients with acute pancreatitis is hypoxemia. Approximately two-thirds of patients will develop tachypnea, mild respiratory acidosis, and hypoxemia during the first 48 h following admission *(176)*. In these patients, physical examination is normal, and abnormalities in chest radiographs are infrequently seen. Approximately one-half of patients demonstrate arterial oxygen tensions of 71 mmHg or below. Severe hypoxia, defined as arterial PO_2 of <60 mmHg, was found in one study in up to 45% of patients *(177)*. This same study also found that those patients with arterial oxygen tensions of less than approx 50 mmHg had a mortality rate of more than 30%. A right to left intrapulmonary shunting of up to 30% of cardiac output as a result of ventilation and perfusion mismatch is thought to be the major cause of hypoxia *(178)*.

Patients who are experiencing their first attack of acute pancreatitis are more likely to develop hypoxia compared to those individuals with a history of previous attacks; the reason for this is unknown. No correlation has been established between the hypoxemia found in these patients and patient age, severity of the attack, pancreatic enzyme activities, serum calcium concentrations, amount of fluid or blood products administered, or estimated fluid sequestration *(150,164)*.

Patients with hypoxemia who show both clinical and radiographic abnormalities of respiratory function may be categorized as reaching stage II. The most common radiographic abnormalities include pulmonary infiltrates or atelectasis, pleural effusions, and pulmonary edema. Patients who reach this stage experience considerably higher morbidity and mortality compared with those in stage I.

Pleural effusions are usually small; however, massive effusions have been described in patients with pancreatitis attributed to ethanol abuse *(179)*. Biochemically, the effusions are characterized by increased amylase activities of up to 30 times greater than corresponding serum activities, protein concentrations >30 g/L, and a fluid:serum LD ratio >0.6 *(172)*. Most pleural effusions are absorbed spontaneously following resolution of pancreatic inflammation.

Patients who exhibit severe dyspnea and extreme hypoxemia that is refractive to increased inspired oxygen concentrations are classified as having stage III respiratory complications. The most serious respiratory complications is the adult respiratory distress syndrome. Not only does acute pancreatitis cause acute respiratory distress syndrome, but the syndrome can exacerbate existing pancreatic injury *(180)*. Thus, a cycle of pancreatic and respiratory injury is created, which if unchecked, can quickly lead to multiple organ system failure. The association of adult respiratory distress syndrome is present in up to 20% of patients with acute pancreatitis with a mortality rate of approx 50%. Adult respiratory distress syndrome typically occurs between 48 h and 1 wk following the onset of acute pancreatitis. Autopsy findings show that the morphological changes seen in the lungs cannot be differentiated from those seen in patients with adult respiratory distress syndrome owing to other pathogenesis, including shock, sepsis, and severe trauma. The incidence of adult respiratory distress syndrome is highest in patients with hemorrhagic pancreatitis, although patients with interstitial edematous pancreatitis are also at risk.

A variety of mechanisms have been postulated in the pathogenesis of respiratory failure in patients with acute pancreatitis. The most frequently cited mechanism involves the release of large quantities of proteases from the inflamed pancreas; they enter the circulation following pancreatic injury and include trypsin, chymotrypsin, and elastase. The release of proteases can cause the breakdown of cellular constituents, pulmonary surfactant, and elastic tissue. In addition, activated proteases can cause the activation of the coagulation and complement cascades.

Another enzyme that has been implicated in the pulmonary damage seen in these patients is PLA. PLA is a lecithinase that cleaves one fatty acid from lecithin, the principal component of pulmonary surfactant, to form lysolecithin and free fatty acids. In addition to the effect of PLA in destroying pulmonary surfactant, the enzyme may also cause breakdown of the phospholipid layer of cell membranes resulting in cell lysis. The action of arachidonic acid formed by the action of PLA on the cell membrane phospholipids may result in the generation of thromboxane A_2, causing increased leukocyte adherence and leukocyte-dependent vascular injury to the lung. Also, the liberated free fatty acid may contribute to further injury. Owing to the potential adverse effects of PLA present in the circulation, this enzyme is considered to play a major role in the pathogenesis of pulmonary injury.

Another mechanism that may play a role in pulmonary injury involves activation of the complement cascade. Some complement fragments, especially C5a, are leukotactic and may cause entrapment of leukocytes within the lung. Activated neutrophils within the lung can produce pulmonary damage owing to release of lysosomal enzymes, generation of oxygen free radicals, or release of arachidonic acid metabolites.

The presence of fibrin and platelet microthrombi in the pulmonary vessels observed at autopsy of patients dying from acute pancreatitis suggests that pulmonary intravascular coagulation and platelet aggregation had occurred. Fibrinogen and platelet concentrations have been observed to be decreased in patients with pancreatitis. Activation of the coagulation cascade may occur as a result of release of trypsin into the circulation. Studies in animals suggest that iv administration of either lipase or PLA substances, both of which that are also present in patients with acute pancreatitis, does not produce thrombosis *(166)*.

A variety of other factors in addition to release of trypsin may contribute to the formation of microthrombi in patients with acute pancreatitis. These factors include acidosis, circulatory shock, and the inhibition of fibrinolysis secondary to the inhibition of plasminogen activation.

Many studies have indicated a role for the generation of free fatty acids following lipolysis in the pulmonary damage seen in acute pancreatitis *(181)*. A high incidence of hypertriglyceridemia has been noted in patients with respiratory failure, suggesting that increased serum triglyceride concentrations may play an etiologic role in the development of pulmonary insufficiency.

Hypertriglyceridemia is often seen in individuals without pulmonary injury, suggesting that hypertriglyceridemia by itself is not responsible for pulmonary insufficiency. Experimental studies suggest that lipoprotein lipase that is present in high concentrations within the pulmonary capillaries may become activated. The activated lipoprotein lipase can cleave fatty acids from triglycerides, causing the release of large quantities of free fatty acids within the lungs. The unbound fatty acids can induce injury to the alveolar membrane, leading to an increase in pulmonary extravascular water, interstitial and intra-alveolar edema, and intrapulmonary shunting *(181)*.

One final mechanism that may play a minor role in pulmonary injury is activation of the kallikrein-kinin system, leading to the production of bradykinin from kininogen. Acute pancreatitis results in the liberation of kallikrein and trypsin from the pancreas; they are probably responsible for the generation of bradykinin from its precursors. The ability of bradykinin to increase lung vascular permeability in patients with acute pancreatitis is small and does not play an important role in the lung injury seen in these patients.

Cardiovascular Complications

Cardiovascular disturbances found in patients with acute pancreatitis include electrocardiographic abnormalities, hemodynamic disturbances, and pericardial effusion. The changes in cardiac function in patients with acute pancreatitis have not been found to be associated with structural abnormalities within the myocardium, suggesting that myocardial depression in acute pancreatitis is of metabolic origin. A variety of biochemical mediators that have profound effects on the cardiovascular system have been described in these patients. Increases in vascular permeability owing to formation of bradykinin and increases in prostaglandins with a decrease in systemic vascular resistance have been described *(182,183)*. The existence of a myocardial depressant factor released from the acinar cells in patients with acute pancreatitis has also been suggested *(184)*.

Electrocardiographic changes in acute pancreatitis are relatively common. Arrythmia, conduction abnormalities, and changes in the T wave and QT period are frequently seen *(185)*. ST elevation is a rare occurrence in these patients. Several hypotheses have been proposed to explain these changes. Electrolyte abnormalities, such as hypokalemia, hypocalcemia, and hyponatremia, are common in acute pancreatitis, and can modify the repolarization phase on the electrocardiogram. Electrocardiographic changes may also be induced by hemodynamic disturbances, such as profound hypotension causing myocardial ischemia, and conduction disturbances. These changes have been especially

noted in patients with pre-existing cardiac abnormalities and cardiomyopathy secondary to ethanol abuse *(186)*.

Hypovolemia occurs early in the course of an attack of acute pancreatitis and is associated with poor prognosis *(187)*. With aggressive volume replacement therapy, hypovolemia is now an infrequent complication of acute pancreatitis. Hypovolemia develops owing to loss of fluid into the peripancreatic spaces and systemic tissues. Fluid loss is owing primarily to an increase in the permeability and a decreased resistance in the peripheral circulation. These effects may be induced by the release of vasoactive peptides, such as bradykinin. In addition, the development of hypoalbuminemia, nausea with vomiting, and sequestration of fluid within the bowel may further contribute to volume loss.

Gastrointestinal disorders presenting with epigastric pain are an important part of the differential diagnosis of acute myocardial infarction. The mistaken diagnosis of acute myocardial infarction in a patient with acute pancreatitis can result in serious consequences owing to withholding of appropriate therapy or initiation of inappropriate measures, such as thrombolytic therapy; the latter given to a patient with acute pancreatitis can exacerbate the underlying disease process *(188)*.

Renal Complications

Acute renal failure is an infrequent, although serious, complication of acute pancreatitis. Mortality in patients who reach this state still remains approx 80%. The extent of tubular necrosis has been shown to be related to the degree of pancreatic inflammation, and is most severe in patients with pancreatitis caused by biliary obstruction or following postoperative complications *(189)*.

Renal failure was believed to be caused by hypovolemia and hypotension alone. However, other factors also play an important role. Some studies suggest that a hypercoagulable state, possibly enzyme-induced, may be an important factor in the pathogenesis of renal insufficiency. Histologic findings of prominent deposits of IgG, fibrin, and fibrinogen in the glomerular capillaries lend support to this hypothesis.

Another mechanism that may also play a role in renal failure involves the release of platelet-activating factor from the ischemic pancreas inducing the release of platelet-activating factor that owing to its potent vasoactive properties, causes a marked decrease in renal blood flow and glomerular filtration rate through either constriction of vascular smooth muscle cells or mesangial cell contraction.

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis in association with acute pancreatitis is a rare complication. Fat necrosis is not localized to any one specific area, and may be found on the buttocks, thighs, upper arms, and trunk. Fat necrosis can accompany pancreatitis in association with malignancy, trauma, and biliary obstruction; however, it appears to occur more frequently in men with pancreatitis attributed to alcohol abuse.

Joint lesions involving the metatarsal, interphalangeal, wrist, knee, and ankle joints are often associated with subcutaneous fat necrosis *(190)*. The joint lesions are clinically identical to gout. However, serum uric acid concentrations may not be increased.

The significance of these lesions is that in some patients with acute pancreatitis, they are the patient's only complaint on presentation *(191)*. The pathogenesis of sub-

cutaneous fat necrosis is poorly understood. It has been postulated that these lesions occur secondarily to the release of active pancreatic enzymes into the circulation or lymphatic drainage. Lipase has been implicated in reports of strongly positive intracellular staining of adipocytes with an MAb specific for pancreatic lipase *(192)*. A more likely explanation for the development of these lesions is that subcutaneous fat necrosis and joint lesions develop in those patients who are deficient in protease inhibitors, such as α-1-antitrypsin and α-2-macroglobulin. Thus, in these patients, circulating active proteolytic and/or lipolytic enzymes would be able to exert their effects in systemic sites. This mechanism would help explain why this syndrome is so rare, in contrast to the relative frequency of pancreatitis. It would also explain why these lesions occur in some patients who are otherwise asymptomatic for pancreatic disease.

Pancreatitis and Multiple System Organ Failure

Multiple system organ failure associated with acute pancreatitis is very similar to that seen in patients with trauma, burns, or other catastrophic illness. Advances in supportive care have increased the number of patients who survive the acute phase of the disease. However, in a minority of patients, acute pancreatitis progresses to multiple system organ failure with poor prognosis. The prevalence of multiple system organ failure in acute pancreatitis is approximately 20% *(187)*, and the mortality rate is proportional to the number of organs involved. In patients with four organ systems failing, mortality is virtually 100%. One study found that the mean number of organ system failures in survivors was 1.4 vs 3.2 in patients who did not survive *(193)*.

The development of organ failure has been shown to be influenced by factors, such as the patient's age, local complications, pre-existing diseases, and systemic infection. Of these factors, systemic infection has been shown to be an important initiating factor for the development of multiple organ system failure *(187,194)*. The predominance of enteric Gram-negative bacteria in both local and systemic infections in patients with acute pancreatis suggests that translocation of intestinal flora from the gastrointestinal tract may be primarily responsible in the pathogenesis of infection and multiple organ system failure *(187,195)*. Studies in animals have shown that reducing the amount of intestinal flora can significantly improve survival in acute pancreatitis. Unfortunately, data for humans with acute pancreatitis confirming these results is lacking.

Pancreatitis-Associated Retinopathy

Retinal lesions in association with acute pancreatitis are a rare complication, being first documented and described in 1975 *(196)*. The retinal lesions are similar to these described by Purtscher in 1910 *(197)* in patients with head trauma in whom sudden loss of vision occurred within hours following injury. The severity of visual impairment can vary widely ranging from complete recovery to permanent impairment. No specific therapy is known.

The mechanism of trauma-induced retinopathy is thought to be owing to retinal ischemia produced by arterial occlusive disease. The exact cause of ischemic retinal injury in patients with acute pancreatitis has not been identified. Initially, obstruction of retinal arteries by fat emboli was the purported mechanism. Evidence for this included the finding of fat emboli in some patients with retinopathy owing to causes

other than pancreatitis, and because arterial fat emboli have been found in other organ systems in patients with acute pancreatitis.

Recent studies suggest that other mechanisms are responsible for the retinopathy of acute pancreatitis. One hypothesis involves the generation of activated complement factor 5 by proteolytic enzymes released from the inflamed pancreas *(198)*. The active factor 5 can induce the aggregation of granulocytes leading to microvascular occlusion by microemboli. However, this mechanism alone cannot account for all cases of pancreatitis-associated retinopathy.

A fairly strong relationship has been found between retinopathy in acute pancreatitis and excessive ethanol consumption. However, the association between the two is not well understood. It has been suggested that a nutritional deficit, toxin exposure, or some other risk factor associated with alcohol ingestion or alcoholism may be responsible *(198)*.

The development of retinopathy has been found by some to have prognostic significance *(199)*. Retinopathy was four times more frequent in patients with multiple system organ failure than in those without any organ system failure. In addition, the frequency of retinopathy in nonsurvivors was twice that seen in survivors. Thus, the retinopathy of pancreatitis may have prognostic significance; its onset indicates a poor prognosis and the likelihood of development of multiple organ system failure.

SUMMARY

Biochemical Indicators

Measurement of amylase activity in serum has remained the primary biochemical test for the evaluation of patients with suspected acute pancreatitis for over 80 yr. Even with its acknowledged shortcomings, including nonspecificity for the pancreas and increases in patients with renal insufficiency, amylase remains one of the top 20 most commonly requested laboratory tests. Attempts to improve the nonspecificity of amylase have led to methods for the measurement of amylase isoenzymes. Increases in the amount of P type amylase on the presence of the P3 isoform have been advocated as more specific markers of pancreatic damage. However, use of amylase isoenzymes on the P3 isoform have been found to provide similar diagnostic accuracy to that of lipase alone.

Lipase is often considered to be the most useful marker of acute pancreatitis available today. Previous problems with the analysis of lipase have been largely overcome by the use of colipase which is an important cofactor for the enzyme. Measurement of lipase in conjunction with amylase may be useful in the evaluation of the pathogenesis of acute pancreatitis. Calculation of the ratio of lipase to amylase has been found by some to allow differentiation of pancreatitis owing to ethanol abuse from other causes; the ratio of lipase to amylase being much higher in ethanol-induced pancreatitis.

Lipase has recently been shown to be composed of two isoforms, L1 and L2, which are probably posttransitional variants of a single enzyme form. Preliminary studies have shown the diagnostic accuracy provided by measurement of the L2 isoform to be better than that provided by total lipase activity.

In addition to amylase and lipase, several other biochemical markers of acute pancreatitis have been evaluated for their effectiveness in detecting pancreatic injury.

Assays have been developed for trypsin, phospholipase A, and carboxypeptidase A. Although these markers may provide greater diagnostic accuracy for acute pancreatitis than amylase or lipase, and may even allow for the severity of an attack to be determined, none of these markers have been implemented to any great extent.

Etiology of Acute Pancreatitis

A great number of etiologic factors have been recognized with the potential of initiating acute pancreatitis. Drug-induced pancreatitis has been attributed to more than 50 drugs. Therapy with ddI has most recently been implicated as a causative agent of acute pancreatitis. This compound is frequently used in patients with AIDS. Acute pancreatitis associated with patients taking ddI has been reported with an incidence of 4–23.5%.

Metabolic disturbances implicated in causing acute pancreatitis include hypercalcemia and hypertriglyceridemia. Prolonged or excessive increases in calcium concentrations has been associated with cell damage in many tissues, including the pancreas. A variety of factors have been found that lead to increases in acinar cell calcium concentrations. These initiating factors include ethanol abuse, hyperlipidemia, ductal hypertension, and certain drugs and toxins.

Hypertriglyceridemia is well-recognized as a cause of acute pancreatitis. Hypertriglyceridemia may be genetic in origin or it may be secondary to various causes including ethanol abuse, diabetes, hypothyroidism, nephrotic syndrome, or certain drugs. Mechanisms of hypertriglyceride-induced pancreatitis include chemical irritation caused by the release of cytotoxic free fatty acids or increases in acinar cell calcium concentrations as discussed previously.

Postoperative pancreatitis has been described in patients undergoing abdominal surgery as well as following surgery not involving the abdomen. Factors thought responsible for postoperative pancreatitis include direct pancreatic injury in patients undergoing abdominal surgery; pancreatic ischemia, especially in patients placed on cardiopulmonary bypass; use of perioperative medications such as calcium replacement therapy; the production of microthrombi with resultant pancreatic ischemia, pancreatic duct obstruction; and infarction. Pancreatitis associated with ERCP has been reported to occur in up to 5% of individuals undergoing this procedure. The incidence of hyperamylasemia in patients undergoing this procedure has been reported to be as high as 70%.

The association between ethanol abuse and acute pancreatitis has been known for well over a century. Ethanol induced pancreatitis usually develops following chronic ingestion of alcohol for at least 7–10 yr. Several theories have been proposed to explain the pathogenesis of ethanol-induced pancreatitis. These mechanisms include alcohol-induced stenosis of the sphincter of Oddi, the production of free radical compounds following the metabolism of ethanol, and a reduction in pancreatic blood flow mediated by ethanol.

Anatomic abnormalities have also been reported to cause acute pancreatitis. Pancreas divisum is the most common anatomic variant of the pancreas and has been implicated by some as the source of 10–20% of cases of pancreatitis for which no other causes can be found. Other anatomic abnormalities that may predispose an individual to pancreatitis include dysfunction of the Sphincter of Oddi and ampullary stenosis.

Pancreatitis owing to biliary obstruction has been reported as the most common cause of pancreatitis in women, with ethanol being the most common cause in men. The most common cause of biliary obstruction is caused by gallstones. However, obstruction can be also be the result of tumors or parasites.

Assessment of Severity of Acute Pancreatitis

Assessment of the severity of acute pancreatitis plays an important role in the treatment plan. Severity assessment helps ensure that intensive therapy is targeted at patients with the severest attacks and allows the early detection of complications. Many schemes have been developed for use in gauging disease severity. Those include clinical assessment, multiple prognostic criteria, peritoneal tap, computerized scanning, and use of biochemical test results.

Severity assessment based on clinical assessment is often inaccurate, especially when performed early in the course of the disease. The use of multiple prognostic criteria has gained greater acceptance. Classification of disease severity by use of multiple prognostic criteria include that of Ranson, the Glasgow score, the APACHE and APACHE II scores, and the simplified acute physiology score. Studies have demonstrated that the APACHE II score is superior to these other classification schemes.

A more simplified approach for classifying patients with respect to disease severity relies on the use of single prognostic indicators. A variety of enzymes and other protein markers have been suggested for this purpose. These markers include neutrophil elastase, C-reactive protein, trypsinogen activation peptide, pancreatitis-associated protein, complement, interleukin-6, tumor necrosis factor, ribonuclease, antiproteases including α-2-macroglobulins and α-1-antitrypsin, phospholipase A_2, and methemalbumin. Other single prognostic indicators include the peritoneal tap and determination of the body mass index.

Complications of Acute Pancreatitis

Acute pancreatitis can result in the release of a wide array of biochemical substances that can induce a variety of derangements, both local and systemic. Local complications include hemorrhage, pseudocyst, pancreatic abscess and phlegmon.

Biochemical disturbances that can occur as a result of acute pancreatitis may be primarily responsible for initiating major organ failure in severe attacks. These disturbances include hypocalcemia, hypomagnesemia, hyperlipidemia, and hyperglycemia. Coagulation disturbances range from scattered intravascular thrombolysis to fatal disseminated coagulation.

Severe cases of acute pancreatitis are often complicated by multisystem organ failure. Organ systems most commonly affected include the renal, pulmonary, and cardiovascular systems. Pulmonary injury has been described in up to 70% of patients with acute pancreatitis. A variety of mechanisms may be responsible for the pathogenesis of respiratory failure. The most frequently cited mechanism involves the release of large quantities of proteases from the inflamed pancreas. Activation of the complement cascade may result in recruitment of neutrophils within the lung and damage due to release of lysosomal enzymes. Another mechanism for pulmonary injury may involve activation of lipoprotein lipase within the pulmonary capillaries with cleavage of fatty acids from the increased concentrations of triglycerides seen in these patients.

Cardiovascular disturbances seen in patients with acute pancreatitis include electrocardiographic abnormalities, hemodynamic disturbances, and pericardial effusion. Electrocardiographic changes have attributed to electrolyte abnormalities and hemodynamic disturbances.

Renal complications are an infrequent although serious complication of acute pancreatitis. Factors suggested to play a role include a hypercoagulable state and the release of platelet-activating factor which causes a marked decrease in renal blood flow. Other complications associated with severe cases of acute pancreatitis include subcutaneous fat necrosis, joint lesions involving the metatarsal, interphalangeal, wrist, knee, and ankle, and pancreatitis-associated retinopathy.

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