
Acute Pancreatitis and Normoamylasemia

Not an Uncommon Combination

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A consecutive series of 352 attacks of acute pancreatitis (AP) was studied prospectively in 318 patients. AP was ascertained by contrast-enhanced CT scan in all but four cases in which diagnosis was made at operation or autopsy. Sixty-seven of these cases (19%) had normal serum amylase levels on admission (*i.e.*, less than 160 IU/L, a limit that includes 99% of control values), a figure considerably higher than generally admitted. When compared to AP with elevated serum amylase, normoamylasemic pancreatitis was characterized by the following: (1) the prevalence of alcoholic etiology (58% *vs.* 33%, respectively, $p < 0.01$), (2) a greater number of previous attacks in alcoholic pancreatitis (0.7 *vs.* 0.4, $p < 0.01$); and (3) a longer duration of symptoms before admission (2.4 *vs.* 1.5 days, $p < 0.005$). In contrast AP did not appear to differ significantly in terms of CT findings, Ranson's score, and clinical course, when comparing normo- and hyperamylasemic patients, although there was a tendency for normoamylasemic patients to follow milder courses. Serum lipase was measured in 65 of these normoamylasemic cases and was found to be elevated in 44 (68%), thus increasing diagnostic sensitivity from 81% when amylase alone is used to 94% for both enzymes. A peritoneal tap was obtained in 44 cases: amylase concentration in the first liter of dialysate was greater than 160 IU/L in 24 cases (55%), and lipase was greater than 250 U/L in 31 cases (70%). Twelve of these 44 cases had low peritoneal fluid and plasma concentrations for both enzymes. Thus little gain in diagnostic sensitivity was obtained when adding peritoneal values (96%) to serum determinations. AP is not invariably associated with elevated serum amylase. Multiple factors may contribute to the absence of hyperamylasemia on admission, including a return to normal enzyme levels before hospitalization or the inability of inflamed pancreases to produce amylase. Approximately two thirds of cases with normal amylasemia were properly identified by serum lipase determinations. AP does not appear to behave differently when serum amylase is normal or elevated, and should therefore be submitted to similar therapeutic regimens in both conditions.

DESPITE THE COMMON ADAGE that "a normal value of serum amylase is so rare in cases of acute pancreatitis (AP) that the diagnosis should

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be questioned,"¹ cases of unsuspected AP found at laparotomy or even at autopsy have been reported²⁻⁷ and suggest that the disease can exist without elevated serum amylase levels.

The purpose of this prospective study is to define the incidence of AP with normal amylasemia on admission by the systematic use of contrast-enhanced CT scan, which represents to date the best imaging technique for the pancreas.^{1,6-8} CT scan was performed within 36 hours in all patients *suspected* of having AP. Both groups, *i.e.*, AP with normal and elevated serum amylase, were compared in terms of etiology, number of previous attacks, duration of symptoms, prognostic CT grading, Ranson's score, and outcome. Other enzymatic determinations were considered to see if they could advantageously supplement fallacious serum amylase findings.

Patients and Methods

Between January 1984 and March 1988, 318 patients with AP were admitted to the Clinic of Digestive Surgery of the Geneva University Hospital: 294 patients sejournd once, 17 twice, and 7 three times or more, which totalled 352 attacks of AP. Excluded from this series are cases of established chronic pancreatitis according to the recent classifications^{9,10} (*i.e.*, pancreatic calcifications, dilatation of the pancreatic duct, or evidence of exocrine pancreatic insufficiency) or cases of pancreatitis after surgical or endoscopic procedures on the pancreas.

The diagnosis of AP was established in all cases by contrast-enhanced CT scan performed within the initial 36 hours of hospitalization, except in four cases in which the diagnosis was not established before operation (in three) or autopsy (in one). CT was performed with a third-gen-

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eration Siemens scanner (Erlanger, FRG; 125kV; 230mAs; acquisition time, 4 seconds) after both intravenous and oral administration of contrast media. Eight millimeter sections were taken from the level of the diaphragm to the third lumbar vertebra or further down in the presence of abnormal findings. Diagnostic criteria for pancreatitis included a locally or diffusely enlarged pancreas. Enhancement was harmoniously decreased in edema, while phlegmon or necrosis appeared as heterogeneous avascular areas. Extrapaneatic spreads (EPS), when present, were analyzed in terms of density, extent, homogeneity, enhancement, and localization. In accordance with our previous report,⁷ EPSs were defined as edematous or phlegmonous and three groups were considered: CT group I showed no phlegmonous EPS; CT group II showed phlegmonous EPS in one or two areas; and CT group III showed phlegmonous EPS in three areas or more.

A modified Ranson's prognostic score,¹¹ omitting serum LDH levels, was calculated in all but the four cases mentioned earlier and included the following criteria: age more than 55 years for men and more than 60 years for women; admission leucocyte count more than 16,000 cells/mm³, glycemia more than 11.1 mmol/L, sGOT (AST) more than 120 IU/L; and during the subsequent 48 hours, hematocrit fall more than 10%, blood urea nitrogen increase more than 18 mmol/L, serum calcium less than 2 mmol/L, arterial oxygen pressure less than 8.4 kPa, base deficit more than 4 mmol/L, and fluid sequestration more than 6 L.

Clinical course was assessed in terms of severity and three groups were considered. Mild attacks (n = 220, 62%) evolved without complications other than pseudocyst(s) resolving spontaneously. Severe attacks (n = 101, 29%) developed local or systemic complications that required percutaneous CT-guided drainage, surgery, or intensive care; parenteral nutrition lasting for more than 15 days was also considered within this subgroup. Necrotizing pancreatitis was demonstrated at operation and/or autopsy in all cases resulting in death (n = 31, 9%).

Amylase was measured spectrophotometrically in serum and peritoneal fluid by a chromogenic assay using *p*-nitrophenol oligosaccharides (substrate Testomar, Behringwerke, Marburg, West Germany).¹² When plasma was lipemic, serial dilutions were used for amylase determination. Reference values for serum amylase ranged from

5 to 160 IU/L and included 99% of 178 controls.¹³ Serum amylase was determined on admission and at least four times during the hospital stay. Serum and peritoneal lipase was determined by a turbidimetric method that assays trioleine degradation.¹⁴ The reference values for lipasemia were 0 to 250 U/L. Serum lipase was measured on admission in all but two cases of normoamylasemic AP. Peritoneal amylase and lipase were determined in the first liter of dialysate (isotonic saline), which incubated for approximately 6 hours.

Four causes of AP were identified: biliary lithiasis confirmed by ultrasonography, CT scan and/or surgery; alcohol; postoperative causes; and idiopathic causes when no other cause could be found (Table 1).

Management of AP consisted of nasogastric suction and fluid replacement. Percutaneous peritoneal lavage using 12 to 24 L of isotonic saline per day was performed in all cases unless contraindicated by a previous laparotomy, the palpation of an abdominal mass, or an important dilatation of the transverse colon seen on a plain abdominal x-ray or CT scan.¹⁵

Chi square with Yates' correction or Fisher's exact test according to the sample size and other nonparametric tests were performed by using the SPSS-X package.¹⁶

Results

Pancreatitis with and Without Elevated Serum Amylase

Sixty-seven of the 352 attacks of AP (19%) had serum amylase values at admission of less than 160 IU/L. Fifty of these attacks occurred in men (75%) and 17 in women (25%), with ages ranging from 23 to 80 years (median age, 48.5 years; men 45 years, women 59 years). Within the hyperamylasemic group (n = 285), there were 160 men (56%) and 125 women (44%) ranging in age from 19 to 87 years (median age, 52 years; men 46 years, women 60 years).

Duration of symptoms before admission. Median duration of symptoms before admission was longer in cases of normoamylasemic AP than in hyperamylasemic AP: 2.4 days (4 hours to 16 days) vs. 1.5 days (1 hour to 12 days); (p < 0.005, Mann-Whitney test). The difference was more significant still if etiology was biliary (1.8 vs. 0.8 days; p < 0.001) rather than alcoholic (2.5 vs. 2 days; p < 0.01). All eight cases of normoamylasemic biliary pancreatitis with pain for more than two days before ad-

TABLE 1. *Etiology of Acute Pancreatitis*

Serum Amylase at Admission (n)	Alcoholism (%)	Biliary Lithiasis (%)	Postoperative (%)	Idiopathic (%)	Others* (%)
Normal (67)	39 (58)	12 (18)	4 (6)	10 (15)	2 (3)
Elevated (285)	93 (33)	107 (38)	14 (5)	65 (23)	6 (2)
Total (N = 352)	132 (38)	119 (34)	18 (5)	75 (21)	8 (2)

* The column "others" refers to rare etiologies such as hyperlipidemia, hypercalcemia, or ampullary diverticula.

mission had benign clinical courses and hospital stays shorter than ten days.

Etiology (Table 1). Alcohol was incriminated in 39 of the 67 attacks of normoamylasemic AP (58%) and nearly always affected men (35 of 39). Nine of these cases had suffered previously from similar episodes, while twelve others had presented documented bouts of AP. The number of similar previous episodes in these 39 cases of alcoholic pancreatitis averaged 0.7 (from 0 to 4 episodes). Biliary AP occurred in 12 instances (18%), 7 times in women and 5 times in men, and none of them suffered previously from pancreatitis. Hyperlipidemia was found in four attacks (7%), all associated with chronic alcohol abuse. In four other patients (6%), pancreatitis followed an abdominal extrapancreatic operation, while a fifth patient presented with an ampullary diverticulum. Finally the cause of AP was unclear in the remaining ten patients (15%), although elevated gamma GT levels suggest an alcoholic origin in five of them.

In the group of AP with elevated serum amylase, biliary lithiasis (107 of 285 patients, 38%) prevailed slightly over alcohol (93 of 285 patients, 33%). In the latter subgroup, 37 had experienced previous bouts of pancreatitis (an average number of 0.4 similar episode per case). Alcoholic AP was less frequent and the number of previous attacks was significantly lower in the hyperamylasemic group ($p < 0.05$, chi square and Mann-Whitney tests, respectively).

Prognosis according to CT scan and Ranson's Score and clinical course (Figs. 1 and 2). In both grading systems (i.e., CT and Ranson's criteria), AP did not appear to

■ Acute pancreatitis without elevated serum amylase (n=67)
 □ Acute pancreatitis with elevated serum amylase (n=285)

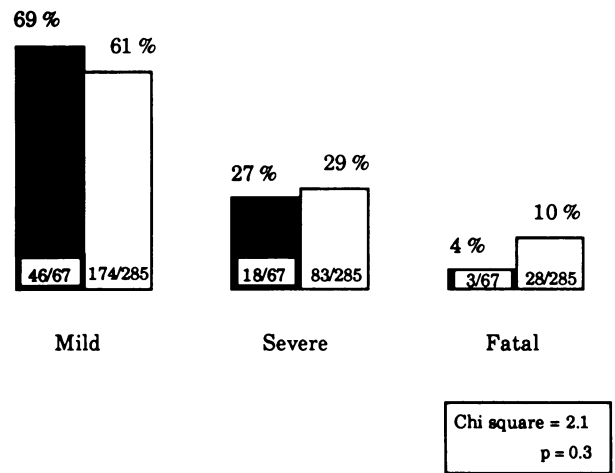


FIG. 2. Clinical course of 352 cases of acute pancreatitis with or without elevated serum amylase.

differ whether amylase was elevated or not, although there was a tendency for normoamylasemic patients to follow a milder course.

Forty-six of the 67 cases of AP with normal amylase (69%) had mild clinical courses. Nine of these developed pseudocysts that were diagnosed between the 8th and 42nd days of hospitalization and which all resolved spontaneously within 3 to 10 weeks.

Eighteen patients (27%) suffered complications. Four developed persistent pseudocysts treated by percutaneous CT-guided drainage alone (in three) or by duodenopancreatectomy (in one). Nine others developed symptomatic infected necrosis requiring laparotomy, necrosectomy, and lavage in eight, and lombostomy in one. Five more suffered systemic complications including multiple organ failure in 2, respiratory failure in 1, renal failure in 1, and severe denutrition in 1. Finally three patients (4%) whose history is described below had fatal outcomes.

A 74-year-old alcoholic man with no history of previous pancreatitis suffered from crampy abdominal pain and vomiting of one-day duration. Examination revealed guarding and slight tenderness of the lower abdomen. White cell count was 22×10^9 /L, serum amylase was 110 IU/L, serum lipase was 200 U/L, and urinary amylase was 50 IU/L. Diagnosis was assumed to be acute diverticulitis. CT scan revealed benign pancreatitis (CT group I) and Ranson's score was 3. No peritoneal dialysis was performed because of a previous laparotomy. He was transferred to the intensive care unit three days later because of respiratory failure. A second CT scan showed a worsening of his pancreatitis. During the following week,

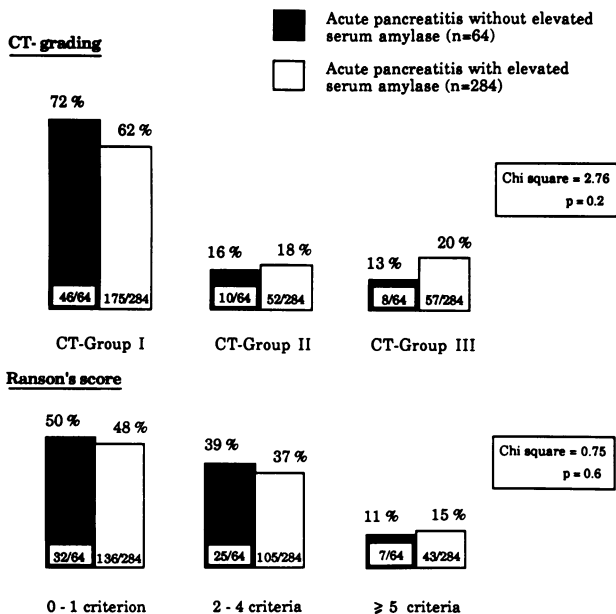


FIG. 1. CT grading and Ranson's score in 348 cases of acute pancreatitis with or without elevated serum amylase. Four cases had neither CT nor complete Ranson criteria because the diagnosis was not made before operation or autopsy.

multiple organ failure with sepsis developed. Phlegmonous EPS was demonstrated on the third CT scan and the patient was operated on: necrosectomy (50 g), cholecystectomy, and jejunostomy brought about a transitory amelioration, although hemodialysis had to be started four days later. A fourth CT scan showed definite aggravation. The second operation showed diffuse necrotizing pancreatitis with leakage from the jejunostomy; necrosectomy (40 g) was performed again. The patient died 16 hours later despite intensive reanimation. Relatives refused the autopsy. Serum amylase and lipase values remained normal during the entire course.

A 55-year-old woman with alcoholic cirrhosis and cardiomyopathy was hospitalized for upper abdominal pain of two days duration. On admission amylase was 85 IU/L, lipase was 310 U/L, urinary amylase was 62 IU/L, and Ranson's score was 2. CT scan showed ascites, a slightly enlarged pancreas, and edema within the mesenteric root and both Gerota fascias. Percutaneous peritoneal lavage was started. Peritoneal determinations of amylase and lipase in the first liter of lavage were 350 IU/L and 700 U/L, respectively. Multiple organ failure developed and she was transferred to the intensive care unit. A second CT scan (day 11) showed a larger pancreas and numerous phlegmons within its head. The third CT scan at 1 month revealed unaltered EPSs but a pseudocyst in the head of the pancreas. The patient was deemed to be inoperable and died on the 44th day of hospitalization. Autopsy disclosed extensive hemorrhagic and necrotizing pancreatitis.

A 62-year-old man with some degree of renal insufficiency due to polycystic kidney disease underwent a subtotal gastrectomy for gastric cancer. Four days after operation he became comatous and developed respiratory failure. No anastomotic leakage was seen on the contrast media meal. Serial determinations of serum amylase and lipase, on postoperative days 1, 3 to 9, and 14 were inferior to 60 IU/L and 400 U/L, respectively. The patient died on day 15 with multiple organ failure. Autopsy revealed diffuse hemorrhagic pancreatitis with retroperitoneal necrosis.

Serum amylase variations during the clinical course. In normoamylasemic pancreatitis, serum amylase rose at least once beyond normal values in 27 of the 67 cases (40%) and exceeded 500 IU/L in 7 (10%). Variations of serum amylase during hospital course were assessed by computing standard deviations (SD) that ran from 20 to 710 IU/L and did not appear to be related to severity of the clinical course (Kruskal-Wallis test). In the group of AP with hyperamylasemia, outcome was not related to initial amylase (ranging from 165 to 4000 IU/L, median 740 IU/L), nor to its variations.

Other Enzymatic Determinations in AP with Normal Serum Amylase

Serum lipase was determined within 24 hours of hospitalization or of onset in cases of postoperative pancreatitis. As shown in Figure 3, two thirds of the cases had increased serum lipase, 20% of them exceeding three times the upper normal value. Urinary amylase was measured in 37 and was found to be normal in 27 (73%), exceeding twice the normal upper value in only one case.

Amylase and lipase were determined in the first liter of dialysis in 44 attacks within the initial 36 hours of hospitalization (Fig. 4). No amylase values higher than 600 IU/L were noted. Although peritoneal lipase was more frequently elevated than peritoneal amylase, this difference was not significant ($p = 0.2$; Mann-Whitney test). On the other hand, 12 attacks (27%) had no increase in serum and peritoneal concentrations for both enzymes. Ten of these 12 attacks had no increase in serum amylase during the whole clinical course. Diagnostic sensitivities achieved by serum and peritoneal enzyme determinations are presented in Table 2.

Discussion

This study was triggered by the observation of rare cases of unsuspected pancreatitis discovered at laparotomy or autopsy and which had presented as acute abdomens. The purpose of this report is to define the true incidence of AP by the systematic use of CT scan performed within 36 hours of admission in any case of abdominal pain suggestive of a pancreatic origin, regardless of amylase

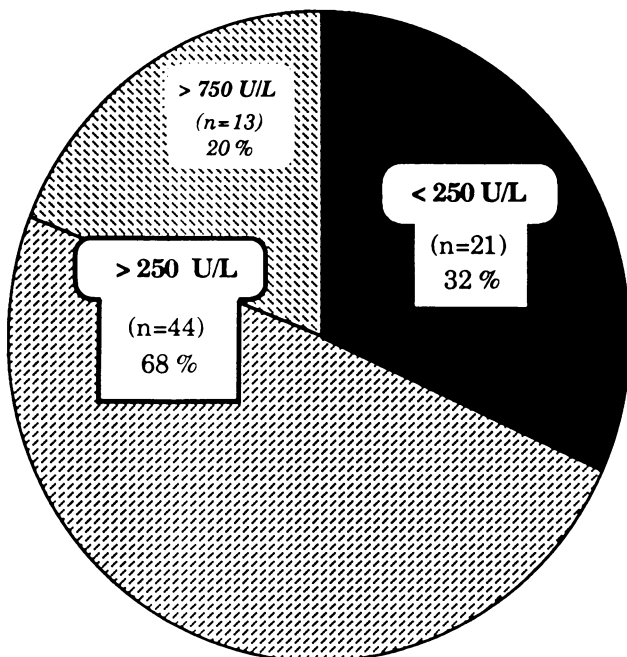
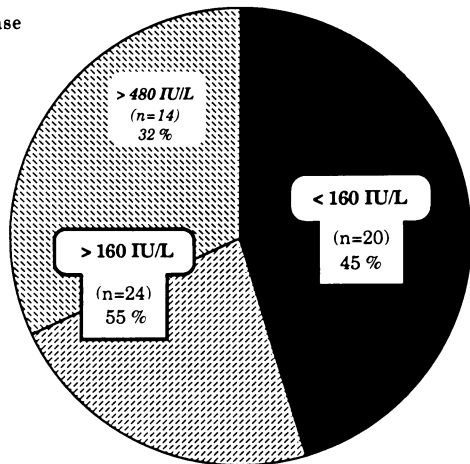
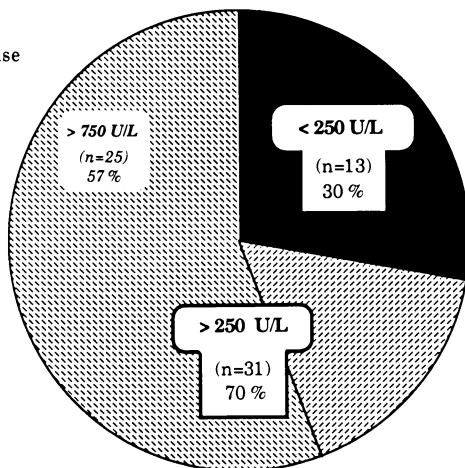


FIG. 3. Serum lipase concentrations at admission in 65 cases of normoamylasemic acute pancreatitis. (Reference values for serum lipase: 0 to 250 UK.)

Peritoneal amylase



Peritoneal lipase



FIGS. 4A and B. (A) Peritoneal amylase and (B) lipase concentrations in 44 cases of normoamylasemic acute pancreatitis.

values obtained on admission (*i.e.*, even when this enzyme was within normal limits). Although expensive, CT scan appears to be the gold standard in AP, as shown by the many authors who use it.^{1,6-8} A recent report from this institution covering 177 cases of AP showed CT to have a 100% specificity (no false-positive findings) and a 92% sensitivity.⁷ The second objective was to see if normoamylasemic AP behaved differently than classical hyperamylasemic pancreatitis. Finally, when available, serum lipase and peritoneal amylase and lipase determinations were evaluated to see if they could unmask normoamylasemic AP.

In the present report, 67 of 352 cases of AP were admitted with normal serum amylase levels. This represents a 19% incidence, a figure significantly higher than commonly admitted.^{1-3,5,6,17,18} In a series of 68 episodes of alcoholic pancreatitis, Spehler et al.⁴ reported a surprisingly high 32% incidence of AP with normoamylasemia.

TABLE 2. Diagnostic Sensitivity of Amylase and Lipase in Acute Pancreatitis

	False-Negative Results	Total	Sensitivity (%)
Serum amylase alone	67	352	81
Serum amylase and lipase	21	350*	94
Serum amylase and peritoneal amylase and lipase	13	329†	96
Serum and peritoneal amylase and lipase	12	329†	96

* Two cases of normoamylasemic AP had no serum lipase determination and were subtracted from the total.

† Twenty-three cases of normoamylasemic AP had no peritoneal enzyme determination and were subtracted from the total.

despite questionable CT imaging criteria and despite the fact that CT confirmation was obtained in only two thirds of their cases.¹⁹ Most, if not all, authors parallel AP with hyperamylasemia with threshold diagnostic levels of serum amylase generally arbitrarily chosen and ranging from one to nine times the upper normal value, the higher factors intended to eliminate more false-positive results.^{1-8,11,15,17,18,20}

Another source of confusion resides in the facts that more than 200 techniques of amylase determination have been described since Magendie's inaugural protocol in 1846 and that no international reference method has yet been adopted.^{20,21}

Why Do Normoamylasemic APs Exist?

There are many reasons to reconcile AP with normal amylasemia on admission. This enzyme is believed to rise within 24 hours after onset of the disease and return to normal within five days.^{1,20-22} In this series duration of symptoms before admission was longer in the group of normoamylasemic patients, the difference being greater in biliary than alcoholic pancreatitis. Studying serum amylase profiles, Hiatt et al.¹⁸ showed that the decrease in amylase occurred significantly faster in biliary than in alcoholic pancreatitis. In the present survey, some patients might well have been admitted after amylase had returned to normal. This seems particularly true for mild biliary pancreatitis resulting from transient papillary stone obstruction.

Another possible explanation is that in relapsing and/or alcoholic pancreatitis, deteriorated parenchyma is no longer able to produce sufficient amounts of enzymes.^{4,9,10,22-24} Even though the distinction between relapsing AP and exacerbation of chronic pancreatitis is sometimes impossible (in fact, absent from recent international classifications of pancreatitis^{9,10}), the 21 attacks with a story of previous similar episodes and alcoholic abuse in the present series did not appear to suffer from chronic pancreatitis because none of them showed pan-

creatic duct dilatation, calcifications on CT scan, or signs of pancreatic exocrine insufficiency.

Some authors have postulated that severe necrotizing pancreatitis may yield falsely reassuring serum amylase levels, as was the case in one patient in this series who died with massive pancreatic destruction after subtotal gastrectomy. However this was not the rule in our study because the two other fatal cases with normal amylase had suffered from relatively mild disease in terms of Ranson's score and CT findings on admission; associated conditions such as advanced age, liver cirrhosis and cardiopathy certainly played an important part. In fact, AP did not appear to be more severe in the normoamylasemic group: the clinical course was deemed difficult in 30% of cases compared to 40% when amylase was elevated.

Finally, in those rare cases of lactescent plasma, false-negative amylase results were circumvented by serial dilution techniques.²⁵

Do Normoamylasemic APs Behave Differently?

Initial serum amylase is usually believed to bear no prognostic significance,^{1,20,22,23,26} although cases of severe AP without hyperamylasemia have been reported.^{2-6,20,26,27} In the experience of Albo et al.,²⁷ for instance, one third of their very ill patients with hemorrhagic pancreatitis had normal amylasemia, suggesting that amylase levels could be inversely related to the severity of the disease. In the present series, when considering CT scan, Ranson's score and clinical course, AP did not behave differently in terms of statistical significance whether amylase on admission was normal or elevated, although there was a tendency for normoamylasemic attacks to follow milder courses. It is likely that most benign normoamylasemic attacks would have been misdiagnosed without the use of CT scan. On the other hand, independent of initial amylasemia, variability of serial serum amylase during the clinical course as assessed by standard deviations was not related to the severity of the disease, a finding previously reported.²³

Can more reliable tests be advocated to detect or confirm AP when serum amylase is not elevated or when CT scan is not available, as is often the case in smaller hospitals? Although quite accurate, immunoreactive trypsin, elastase-1, phospholipase A₂, carboxylic ester hydrolase, and carboxypeptidase determinations are seldom resorted to in the emergency setting due to their complexity.^{1,28-31} Likewise electrophoretic determinations of amylase isoenzymes and the amylase/creatinine clearance ratio, however promising in enhancing the diagnostic specificity of amylase, appear to be of limited value when serum amylase is within the normal range.^{1,29-35} Urinary amylase, considered by some as more sensitive than serum amylase in detecting AP,³⁵ was equally disappointing in our ex-

perience because it was significantly elevated in only one of 37 instances of normoamylasemic AP.

Assaying of lipase, which rises after amylase and remains elevated longer, had not gained wide acceptance.^{1,29,31,35,36} And yet, in the present series, 44 of 65 cases of normoamylasemic AP (68%) had elevated lipasemia, thus increasing diagnostic sensitivity from 81% when serum amylase alone is used to 94% when both enzymes are considered. Lipase is also believed to rise more than amylase in cases of alcoholic pancreatitis.³⁴⁻³⁶ The combined assaying of colipase might enhance the accuracy of lipase determinations.³⁶

Little additional help in diagnosis was obtained when considering peritoneal determinations of both enzymes (from 94% to 96%). Strangely enough peritoneal amylase hyperconcentrations were not necessarily associated with elevated serum levels as if they were too low (less than 600 IU/L) to produce hyperamylasemia.³⁸ Peritoneal absorption is probably not the most important mechanism involved in increasing plasma levels. Recently increased plasma amylase was found to result first from direct venous drainage followed by lymphatic drainage *via* the thoracic duct.³⁹ In our series peritoneal and serum concentrations were better correlated for lipase.

In conclusion these results do not minimize the diagnostic value of serum amylase, which remains the simplest and most readily available test in AP.^{1,7,20-22,28-31} However normal serum amylase levels on admission should not dismiss the diagnosis of AP, and future classifications of pancreatitis mention the fact that hyperamylasemia is not a necessary condition for the diagnosis of AP. Approximately two thirds of cases with normal amylasemia were properly identified by lipase determinations. CT scan should be used in case of doubtful or negative enzymatic results.^{7,31} Finally AP does not appear to behave differently if serum amylase is normal or elevated and should, therefore, be submitted to similar therapeutic regimens in both conditions.

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