Significance of Prolonged Elevation of the Serum Amylase *

FRANK J. VEITH, M.D., ROBERT M. FILLER, M.D., COSTAN W. BERARD, M.D.

From the Surgical Service of the Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts

THE SIGNIFICANCE of the serum amylase determination in the diagnosis of acute pancreatic disease is universally accepted. In typical acute pancreatitis the serum amylase reaches its peak in one to two days and then returns to normal over the next three to five days.[1, 2, 9] There is, however, a small group of patients who present with typical acute pancreatitis in whom the hyperamylasemia persists considerably longer. Since the management and prognosis of such patients depend on the significance of this laboratory finding and since the pertinent literature is scant, we examined a group of patients with pancreatic disease to determine the frequency and significance of protracted elevation of the serum amylase.

Material and Methods

All cases of pancreatic disease occurring at the Peter Bent Brigham Hospital during the years 1948 to 1960 were reviewed; there were 233 cases of acute pancreatitis during this period. Of these only six had elevated serum amylase for more than three weeks. The three-week duration was selected since patients with less prolonged elevations had clinical courses, complications and prognoses similar to the over-all group of patients with acute pancreatitis. In our laboratory amylase determinations were performed by the Somogyi method [15] until August 1958 and the Van Loon method,[16] thereafter. Normal values ranged from 70 to 210 units. For the purpose of this review an elevated serum amylase was defined as one over 300 units in order to rule out minor variations in laboratory technic and to eliminate patients with high normal amylase levels. The six cases of pancreatitis with protracted amylase elevations by these definitions were studied and will be presented (Cases 1–6).

In addition, the laboratory records were reviewed for the same period. In this way two additional cases with protracted hyperamylasemia but without pancreatic disease were discovered and will be presented (Cases 7, 8). Several additional cases with protracted hyperamylasemia associated with and roughly paralleling the azotemia of renal disease were also noted; but since this phenomenon has been observed before,[9-11] these cases are excluded from this report.

Although serum amylase determinations have been performed at the Peter Bent Brigham Hospital since 1925, the period 1948 to 1960 was chosen for review since prior to that period the determination was not employed with sufficient frequency to uncover patients with prolonged hyperamylasemia. Even in the period studied it is possible that additional cases occurred but were undetected.

Case Reports

Case 1. G. D., PBBH 9D818: This 48-year-old white, non-alcoholic woman entered the hospital on 8-19-52, 12 hours after the onset of severe abdominal pain, nausea and vomiting. A diagnosis of acute pancreatitis was made. The amylase rose to a peak of 1,000 units on the third hospital day

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and fell to normal on the seventh hospital day. The clinical manifestations reached a peak severity on the seventh hospital day. The patient was discharged on the 28th hospital day.

She re-entered the hospital three months later on 11-23-52, again with severe abdominal pain and a 207-day hospitalization ensued. This was featured by two periods of prolonged serum amylase elevations. The first, lasting 60 days, was associated with frequent flare-ups of pain following eating. The amylase ranged from 500 to 1,000 units and was usually over 750 units. At laparotomy on the 30th hospital day, the patient had a diffusely enlarged pancreas with thickening and inflammation of the omentum and root of the mesentery. Cholecystectomy, choledochotomy and sphincterotomy were performed. The gallbladder was inflamed although no stones were found. No pancreatic cyst was noted. The operation failed to alter the patient's clinical or laboratory course. Feeding continued to produce exacerbations of abdominal pain and the amylase remained elevated over the next 28 days. A feeding jejunostomy on the 58th hospital day resulted in clinical improvement, and serum amylase fell to normal levels. On the 111th hospital day a cholangiogram produced renewal of abdominal pain and elevation of the amylase. The pain necessitated bilateral low dorsal sympathectomy on the 141st hospital day. However, the pain continued and serum amylase remained between 750 and 1,600 units. On the 170th hospital day drainage of a pancreatic pseudocyst to the exterior produced relief of symptoms and immediate reduction of serum amylase to normal where it remained until the patient was discharged. Serum bilirubin remained normal throughout the patient's hospitalization.

Comment: This patient's first period of protracted hyperamylasemia coincided with smouldering and persistant pancreatitis. The elevated amylase and pancreatitis improved after a feeding jejunostomy which probably decreased pancreatic stimulation. The patient's second period of hyperamylasemia was definitely associated with a pseudocyst, and cyst drainage resulted in a rapid fall of the serum amylase to normal levels.

Case 2. H. F., PBBH 9A328: This 36-year-old, alcoholic man entered the hospital on 12-14-48 with severe abdominal pain, fever and leukocytosis. His admission diagnosis was appendicitis, and he underwent laparotomy at which time acute hemorrhagic pancreatitis with fat necrosis was found. The gallbladder and common bile duct were normal. Postoperatively his serum amylase remained elevated for three days. The patient was discharged from the hospital on the 22nd hospital day.

He was admitted to the hospital for the second time on 11-8-51 with abdominal pain, fever and hyperamylasemia. Serum amylase remained greater than 300 units for three days, fell to normal for ten days and then rose and remained elevated for 33 days in the range of from 400 to 1,120 units. At laparotomy, on 12-22-51, a pancreatic pseudocyst was found and drained. Serum amylase fell precipitously to low normal levels (50 to 60 units) and remained so until the patient's discharge. Serum bilirubin was normal during the patient's hospitalization.

Comment: Persistently elevated amylase in this patient was associated with a pseudocyst. Drainage of the cyst resulted in rapid fall of the serum amylase to normal levels.

Case 3. M. S., PBBH D7611: This 70-year-old white, alcoholic man entered the hospital on 2-15-52 with history for eight weeks of malaise, fever, epigastric fullness, pain and vomiting. He had a left upper quadrant abdominal mass and serum amylase of 840 units on admission. Chemical tests of liver function were normal. The serum amylase remained elevated during the first hospital week. A baseball-sized pseudocyst in the tail of the pancreas was marsupialized on the ninth hospital day. Initially the serum amylase decreased but not to normal until the 24th hospital day. It remained normal until discharge on the 34th hospital day.

Comment: Hyperamylasemia in this patient was associated with a pseudocyst. Following drainage of the cyst, the serum amylase level fell slowly. This could be explained by incomplete decompression of the cyst or by persistent but slowly resolving inflammation in the adjacent pancreas.

Case 4. J. W., PBBH 7P535: This 70-year-old white man underwent vagotomy and posterior gastroenterostomy for an obstructing duodenal ulcer on 7-1-60. His preoperative serum amylase and bilirubin had been normal. At operation some induration of the pancreas adjacent to the ulcer was noted. Because the gallbladder was tense and incompressible, a cholecystostomy was performed. Bile in the gallbladder was normal and there were

no stones. His postoperative course was stormy and febrile. The cholecystostomy tube functioned poorly, and on the fourth postoperative day the patient became jaundiced. His serum amylase rose to 445 units on the 17th postoperative day at which time his bilirubin had risen to 7.8 mg.%. A diagnosis of postoperative pancreatitis secondary to ampullary obstruction was assumed. Over the next three weeks (17 to 41st postoperative days) the bilirubin level fell to 3.0 mg.% but the serum amylase ranged between 550 and 1,100 units. At the end of this period cholangiogram through the cholecystostomy tube showed obstruction in the distal common bile duct. This study also showed that the cholecystostomy tube had been functioning poorly because it was in a tract outside the gallbladder. The tube was, therefore, removed. A biliary fistula then developed and persisted over the next five weeks. Nevertheless, the patient ate and felt moderately well. Serum bilirubin remained elevated between 2.0 and 3.0 mg.% and serum amylase fluctuated between 575 and 750 units over these five weeks. Eight weeks after the onset of his hyperamylasemia the patient was again operated upon. A 9.0 cm. mass was felt in the head of the pancreas with induration extending irregularly into the body and tail. The possibility of carcinoma was considered. Because of the risk of pancreatic biopsy and since the extent of the mass precluded curative resection no specimen was removed. A cholecystjejunostomy was performed to relieve ampullary obstruction.

By the second postoperative day the serum amylase level had fallen to 108 units and remained normal thereafter. Serum bilirubin fell to 0.87 mg.% over the next two weeks. The patient remained free of manifestations of pancreatic disease over the subsequent 19 months.

Comment: In this patient the stormy course, jaundice and hyperamylasemia after his first operation in all probability resulted from postoperative pancreatitis brought about by obstruction in the ampullary region of the common bile duct. One might speculate that a stone was impacted in this region by the original operative manipulation. The pancreatic mass could have represented a pseudocyst, although this possibility was unfortunately not investigated at the second operation. However, decompression of the bile ducts resulted in a prompt fall of the serum amylase and resolution of the pathologic process within the pancreas to the extent that the patient has remained well for over one and one-half years. The probability, therefore, is much greater that the mass was a benign process rather than a carcinoma.

Case 5. B. J., PBBH 6M654: This 30-year-old, nonalcoholic negro woman entered the hospital on 8-27-58 with acute pancreatitis manifested by abdominal pain, fever, tachycardia and serum amylase of 720 units. Despite remission of all signs and symptoms over the following two weeks, the amylase level remained elevated (500–800 units). A left upper quadrant abdominal mass, which had been palpable between the fourth and ninth hospital days, receded. On the 14th day a right upper quadrant mass was first noted. Because of this mass and a persistently elevated serum amylase, the patient was operated upon. The mass proved to be within the head of the pancreas. The gallbladder contained stones, and cholecystostomy was performed. The common duct was thought to contain stones but was not opened because the patient suddenly became hypotensive. Aspiration of the mass was unsuccessful; nevertheless it was thought to be cystic. Postoperatively the serum amylase rose to 1,540 units. Although the patient improved clinically, serum amylase remained elevated (600 to 1,500 units) for five weeks and then gradually fell to normal. Serum bilirubin and alkaline phosphatase determinations were repeatedly normal. The patient was discharged and readmitted one month later for cholecystectomy and choledochotomy. At operation, the entire pancreas was thickened, edematous and enlarged to three times normal size. No cysts, masses, common duct stones, or obstructions were found. Serum amylase remained normal throughout the second hospital stay.

Comment: Protracted hyperamylasemia in this patient was probably due to persistent inflammatory reaction in the pancreas. A pseudocyst was suggested but not proven. The possibility of pancreatic duct obstruction due to an ampullary stone which subsequently passed must be considered but the normal bilirubin and alkaline phosphatase tests make this unlikely.

Case 6. M. J., PBBH 9N454: This 54-year-old Negro alcoholic entered the hospital on 9-20-59 with abdominal pain, fever, nausea and vomiting, and serum amylase of 646 units. He was treated for acute pancreatitis. Although the signs and symptoms subsided within five days, amylase re-

mained elevated (400–700 units). The patient was discharged entirely well after 11 days hospitalization, and has continued well despite marked persistent elevation of the serum amylase for more than three weeks after discharge. Gastro-intestinal x-rays following discharge were normal. Blood urea nitrogen and chemical tests of liver function were normal.

Comment: Persistent hyperamylasemia in this patient was not explained. Partial pancreatic duct obstruction, however, was not ruled out, nor was the possibility of a small undetectable pseudocyst which resolved without treatment.

Case 7. R. A., PBBH 2A500: This 49-year-old white man was admitted to the hospital on 10-17-50 for abdominal pain without elevation of temperature, rate or white blood cell count. Initial serum amylase determinations were normal, and he was thought to have intestinal obstruction secondary to adhesions. Twenty-two days following admission, concomitant with a bout of severe abdominal pain, serum amylase values rose to 689 units and remained elevated (400–800 units) for 34 days. Liver function tests and blood urea nitrogen levels were normal. At this time laparotomy was performed because of a suggestion on x-rays of a lesion producing extrinsic pressure on the lesser curve of the stomach. The liver was cirrhotic; the gallbladder and common bile ducts were normal; the pancreas appeared and felt grossly normal, and a biopsy specimen of the pancreas was interpreted as normal. Liver biopsy specimen showed cirrhosis with interstitial hepatitis. Postoperatively the patient became asymptomatic despite persistent hyperamylasemia until discharge. He has remained well.

Comment: Persistent hyperamylasemia in this patient was not explained. Although intra-pancreatic duct obstruction was not ruled out, there was no gross or microscopic evidence of pancreatitis or its complications.

Case 8. B. K., PBBH 5520: This 82-year-old white, nonalcoholic woman entered the hospital on 7-12-55 with mild right upper quadrant pain and jaundice. She had a history of intermittent right upper quadrant and epigastric pain for two years. Serum amylase was greater than 600 units and other tests were compatible with the diagnosis of obstructive jaundice. A closed liver biopsy specimen showed portal fibrosis and chronic inflammation. The jaundice cleared spontaneously but the serum amylase remained between 600 and 900 units. On the 29th hospital day, the patient underwent laparotomy. The pancreas was normal. The gallbladder was inflamed; it contained stones which were removed. The common bile duct was normal and contained no stones. There was a large duodenal diverticulum adjacent to the ampulla of Vater. Postoperatively the patient did well although serum amylase continued to be elevated. She was discharged on the 18th postoperative day, at which time the amylase level was 743 units. One month later she was asymptomatic, but amylase still was 1,210 units and three months later was 810 units. There was no evidence of pancreatic disease or renal insufficiency. Physical examination and gastro-intestinal x-ray series showed no evidence of pancreatic pseudocyst.

Comment: Persistent hyperamylasemia was not explained in this patient although partial pancreatic duct obstruction, secondary to pressure from the duodenal diverticulum, was a possible explanation. There was no evidence of pancreatitis or its complications.

Discussion

Persistent hyperamylasemia following acute pancreatitis is infrequent, occurring in only six of 233 cases (2.6%). In five of these six patients persistent hyperamylasemia was associated with pancreatic pseudocyst or persistent pancreatic inflammation or both (Table 1). In contrast, in two patients without pancreatic disease, persistent serum amylase elevation had no demonstrable clinical significance. It must be noted, however, that partial pancreatic duct obstruction was not ruled out in those in whom protracted hyperamylasemia was unexplained.

Review of the literature sheds some additional light on the significance of persistent hyperamylasemia. Bockus found that 17 of 24 patients with elevated amylase for more than ten days had significant complications of pancreatitis.[2] Seven had recurrent pancreatitis; four had fibrosis or persistent edema of the pancreas at laparotomy; five had pseudocysts; and one had a pancreatic fistula.

TABLE 1. *Cases in Whom Protracted Serum Amylase Elevations Followed an Episode of Acute Pancreatitis*

Case No.		Cause of Pancreatitis	Duration of Hyperamylasemia (days)	Associated or Etiologic Factors
1	Episode 1	Idiopathic	60	Persistent pancreatitis
	Episode 2	Idiopathic	60	Pseudocyst
2		Alcoholic	33	Pseudocyst
3		Alcoholic	24	Pseudocyst
4		Postoperative Ampullary obstruction	55	Ampullary obstruction ? Pseudocyst ? Persistent pancreatitis
5		Biliary calculi	60	Persistent pancreatitis ? Pseudocyst
6		Alcoholic	33	None known

Only four of Bockus' 24 patients had hyperamylasemia for more than three weeks. Of these, two had pseudocysts, one had persistent pancreatic edema, and one had no known complication of pancreatitis. Shackelford noted a patient whose serum amylase remained elevated for five months following excision of a pancreatic adenoma. After drainage of a pseudocyst, the patient's serum amylase immediately fell to normal.[14] In addition, Abruzzo reported two patients in whom pseudocysts were associated with hyperamylasemia for periods of seven to ten days.[1]

The relationship between pseudocyst and hyperamylasemia is further supported by Brilhart and Priestley who noted elevated serum amylase in 12 of 20 cases of pseudocyst.[3] The effect of treatment on the hyperamylasemia was not reported and in none of these cases was the duration of the hyperamylasemia stated. However, Kalser, Roth and Bockus reported a patient with pseudocyst and hyperamylasemia of unknown duration in whom the amylase dropped to normal levels on two occasions after drainage of the pseudocyst.[7]

Understanding of the mechanisms by which protracted hyperamylasemia occurs in these and our cases can be furthered by a review of the currently postulated pathways by which amylase may enter the blood. This understanding forms a basis for the management of patients with protracted hyperamylasemia, and may shed further light on the pathogenesis of pseudocysts.

Amylase, produced in the pancreatic acini, may enter the pancreatic interstitial fluid either by disruption of the acini or through clefts between acinar cells.[13] From the interstitium enzyme enters the pancreatic venous blood and eventually the portal vein. Alternately pancreatic and peritoneal lymphatics convey the amylase to the blood via the thoracic duct.[5, 12] The enzyme reaches peritoneal lymphatics by leaking from the subcapsular interstitium of the gland into the peritoneal cavity. Thus, increased entrance of amylase into the blood could result either from dissolution of acini due to pancreatitis or from increased intraductal and intra-acinar pressure forcing enzyme rich fluid through the intercellular clefts. Amylase is eventually removed from the blood via the kidneys.[11] The observed serum amylase level represents the balance between the amylase absorbed and that excreted. Hence a patient with renal disease may have hyperamylasemia without increase in the quantity of amylase entering the blood.

On the basis of these facts, it is of interest to speculate on the mechanisms

by which prolonged hyperamylasemia occurred in our patients. Partial pancreatic duct obstruction has been shown to play a vital role in the experimental production of pancreatic pseudocysts.[8] Similarly, obstruction of the pancreatic duct has been implicated in human pseudocysts.[4] Furthermore, it has been shown experimentally that increased ductal pressure secondary to acute pancreatic duct obstruction results in an abrupt rise in serum amylase.[6] We, therefore, propose that protracted hyperamylasemia in our patients having only pseudocysts could have been due to persistently increased intraductal, intracystic and intra-acinar pressure generated by an actively secreting gland with a partially obstructed duct. Furthermore, we suggest that pseudocysts were in part the result of the same state of affairs. However, it must be pointed out that all patients with pseudocysts do not have elevated serum amylase levels[3]; and that, in the period during which our cases were collected, there were six cases of pseudocysts at the Peter Bent Brigham Hospital that did not have protracted hyperamylasemia. These facts point up the complexity of the pathogenesis of pseudocysts and the multiplicity of factors affecting the serum amylase level.

In the patients that had persistent pancreatic inflammation in association with prolonged high serum amylase, continued acinar destruction was the probable means by which the enzyme reached the interstitium of the gland. Of course, some duct abnormality could have accounted for the origin and persistence of the pancreatitis in these patients too.

Because of the high incidence of complications in patients who have prolonged elevation of the serum amylase following acute pancreatitis, a sound approach to such a patient would be as follows: A thorough search should be made for a pseudocyst, both by physical examination and careful gastro-intestinal x-ray studies. If a cyst is found, drainage should be instituted. Pancreatography with relief of duct obstruction should be performed, if feasible, at this time. If the problem appears to be persistent pancreatitis, laparotomy with biliary exploration, pancreatography, and relief of duct obstruction is indicated. In the few cases in whom a pseudocyst cannot be demonstrated and the patient is otherwise well, it is reasonably safe to continue to observe the patient if careful follow up can be obtained.

Summary and Conclusions

In a review of 233 cases of acute pancreatic disease, only six were observed to have significant hyperamylasemia for periods over 21 days.

In three of these six cases, the hyperamylasemia was definitely associated with a pancreatic pseudocyst. In two, such an association was suspected. Persistent pancreatitis was an additional factor associated with the protracted hyperamylasemia in at least two of these six cases. In only one, was the prolonged high serum amylase unassociated with a complication.

Two cases of protracted hyperamylasemia unrelated to pancreatic or renal disease are presented.

Partial pancreatic duct obstruction is suggested as a factor etiologic in the production of protracted hyperamylasemia and pancreatic pseudocyst.

In handling patients with prolonged hyperamylasemia subsequent to acute pancreatitis, one must search for a complication of pancreatitis, particularly a pseudocyst.

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