Pancreatitis and Carcinoma of the Pancreas

Some Aspects of the Pathologic Physiology

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• The physiological phenomena accompanying pancreatic disease in adults are related to the local and generalized reaction of the body to the blockage and/or leakage of the three enzymes—amylase, lipase and trypsin. The measurements of amylase and lipase in the serum are the most reliable criteria in the diagnosis of acute disease. Related changes may include hypocalcemia, hypopotassemia, hyperlipemia, hyperglycemia and decreased renal function.

In chronic pancreatitis, there is less fluctuation in the amounts of the enzymes in the blood. The presence of diabetes mellitus, demonstration of calculi by x-ray, and examination of the stools for excess fat and meat fibers are more important diagnostic guides.

In cancer of the pancreas, function tests using secretin stimulation of the gland followed by an examination of the external secretion or determination of the serum amylase have been used with some success.

THE MORE COMMON pancreatic diseases in adults, such as acute pancreatitis, chronic pancreatitis and cancer, are of most importance. Each of them may cause certain physiologic disturbances which can be measured by laboratory tests and are useful in the diagnosis and treatment of the disease and in determining the prognosis.

The pancreas produces about two liters per day of alkaline juice with a pH as high as 8.5,[17] rich in the enzymes amylase, lipase, trypsin and chymotrypsin. It is the effect of the blockage or leakage of these enzymes plus, in some instances, the destruction of the islets that produces a chain of physiological events which result in a pattern of characteristic departures from normal as determined by laboratory tests.

ACUTE PANCREATITIS

In acute pancreatitis there is the greatest variety of changes capable of measurement.[8] The escape of enzymes from the pancreatic ducts causes damage to tissue, edema, hemorrhage and fat necrosis. This results in local phenomena such as pain, tenderness, nausea and vomiting, segmental ileus and even visible subcutaneous hemorrhage in the flanks. Generalized changes may follow, such as hyperamylasemia, hyperlipasemia, hypocalcemia, hemoglobinemia, serum potassium abnormalities, shock and the alarm reaction.[8] Disturbance of renal function and lower nephron nephrosis have been noted.[8, 23] More recently, changes in the clotting mechanism of the blood have been recorded.[13]

The role of each of the enzymes as it infiltrates the tissue is important. Amylase appears to be innocuous. It is simply absorbed by the blood and eliminated in the urine. The most reliable basis for the diagnosis of pancreatitis is the presence of amylase in the blood and urine. Rarely is the test misleading, if other causes of hyperamylasemia are kept in mind. The other causes include perforation of the stomach or intestine, intestinal obstruction and infarction. In any of those conditions the amylase of the intestinal content can be absorbed but the content of the enzyme in the blood is nearly always less than 500 units, and usually under 300, per 100 cc.[8] Other abdominal conditions occasionally associated with an increase in the amount of amylase in the blood include acute cholecystitis,[18] appendicitis, retroperitoneal tumor[19] and volvulus of the colon. Extra-abdominal disorders such as myocardial infarction, pulmonary disease[28] and dissecting aneurysm may be accompanied by a rise in amylase values in the blood and occasionally have to be considered in differential diagnosis. In renal insufficiency the amount of amylase may rise because it cannot be excreted in normal amounts in the urine. This is especially true in uremia. The status of renal function should always be assayed even in the presence of pancreatitis as it may confuse the picture.

In recent years, another cause of high serum amylase and even of mild pancreatitis has been noted.[3] Morphine and codeine may apparently cause a spasm of the sphincter of Oddi of sufficient degree and persistence that dilatation of ducts and absorption of amylase occur. Even mild pancreatitis has been described in a patient with morphine poison-

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ing. Further investigation may prove that some of the hitherto unexplained elevations in amylase content in the blood are owing to opiate therapy in such diseases as acute cholecystitis, dissecting aneurysm, myocardial infarction and pulmonary disease.

In mumps the salivary amylase is absorbed and the content in the blood may rise as high as it does in acute pancreatitis. As the nature of the disease is obvious, however, this causes no problem in diagnosis unless mumps pancreatitis is suspected. Then determination of the lipase and antithrombin content of the blood may be helpful.

It has been reported that in acute pancreatitis the rise of urinary diastase may lag as much as 24 hours behind the increase of amylase in the blood. Some data, including the author's, indicate this may be true; but in most patients the two are parallel in elevation and subsidence. If the diagnosis is in doubt, both the serum and urine should be tested repeatedly. Well controlled investigation by Dankner and Heifetz[6] indicated that if renal function is normal, the amylase is cleared promptly by the kidney. Dankner and Heifetz also observed that transient impairment of renal function is most likely to occur between 24 and 48 hours after the onset of the disease.

If the pancreas is completely destroyed the amylase values in the blood may be normal within the first 48 hours after onset. In such circumstances other tests may be used—determination of amylase content in peritoneal fluid removed by tap, and of the amount of calcium and antithrombin in the blood. Keith and co-workers[14] noted increased amounts of amylase in the peritoneal fluid for as long as three days after the serum value had returned to normal. They studied fifteen patients in this regard and in three cases no peritoneal fluid was obtained when a tap was made. In studying autopsy material, the author was surprised that the autopsy surgeon noted free fluid in the peritoneal cavity in only one-third of subjects with severe or fatal pancreatitis. The value of the peritoneal tap, when the diagnosis is in doubt, is further enhanced by examination of the fluid for bile pigment and acid content.

Lipase is responsible for fat necrosis, the characteristic gross finding in pancreatitis. It is absorbed and unusual amounts may be present in the blood for several days. According to Comfort and co-workers[4] it remains elevated even after the amylase content has returned to normal. The procedure for the determination of serum lipase is more difficult and time-consuming than that for amylase and therefore has not been so generally used.

The fatty acids formed when neutral fat is split by lipase combine with calcium to form soap. This in turn causes a drain on the serum calcium. In the author's experience, the serum calcium mirrors fairly well the quantity of fat necrosis. In severe damage it is below 8 mg. per 100 cc. of blood, and when below 7 mg. the outcome is usually fatal.[8] When depressed it may return to normal between the fourth and sixteenth day of the disease. Thus, determination of the calcium content of the blood may be helpful in the diagnosis in cases in which the patient is not observed until after the amylase content has returned to normal, or in cases in which there is complete destruction of the gland and amylase levels are normal or subnormal.

Perhaps the most interesting of all and the least understood is the action and fate of trypsin. The site of conversion of trypsinogen to trypsin is not known. But, when disseminated in the tissues, it is the apparent cause of hemorrhage[24] both by its direct necrotizing action on blood vessels and by its tendency to cause thrombosis of veins; thus adding to the anoxia of the tissues, furthering necrosis and obstructing the outflow of blood. Trypsin in proper concentration converts prothrombin to thrombin. This factor, added to the necrosis of vascular endothelium and consequent tendency to the deposition of platelets, would likely cause thrombosis. Partial to complete thrombosis of the pancreatic and splenic veins has been noted many times at necropsy.

Trypsin or trypsin plus lipase is also capable of causing hemolysis; thus hemoglobin may be released in the areas of hemorrhage and absorbed. Twice the author has noted a brown pigment in the serum of patients with severe pancreatic necrosis. One of them had severe oliguria, and lower nephron nephrosis was observed at necropsy.[8] Furthermore, in necropsy material the lesser omental cavity may be greatly distended with brown fluid while abundant gross evidence of hemosiderin is seen in the lining. There is reason, therefore, to believe that local hemolysis resulting in hemoglobinemia does occur in acute pancreatitis.

The fate of any trypsin absorbed by the blood is a problem all of its own. The plasma contains trypsin inhibitor,[25] a specific neutralizing substance which combines with trypsin. The author is now in the process of measuring both of these factors in patients with pancreatitis and various other diseases.

Innerfield and co-workers[13] produced hypertrypsinemia in dogs by the intravenous injection of the commercial trypsin. This caused a decrease in Ac-globulin, prothrombin and antithrombin for about five hours. Then Ac-globulin and prothrombin returned to normal, but the antithrombin rose to excessive levels for 15 to 17 hours. These investigators noted that in patients with acute pancreatitis the antithrombin remained high throughout the course of the acute illness. A similar rise in antithrombin did not occur in other acute abdominal conditions.

In a more recent report they stated that trypsin was present in the blood in each of the patients with pancreatitis.

The author has done the antithrombin tests* on a few patients. The content was normal in one with pancreatitis, increased in a patient with mesenteric thrombosis and also in one with metastatic carcinoma of the liver. It would seem that further experience with the antithrombin test is in order before it achieves the prominence given amylase in the diagnosis of acute pancreatitis.

Since 1846,[26] hyperlipemia with a milky serum has occasionally been noted in acute pancreatitis. This phenomenon is probably owing to more than one cause. Klatskin[15] observed that the course of idiopathic hyperlipemia may be complicated by attacks of acute pancreatitis, owing perhaps to clumped lipid particles in the vascular tree of the pancreas. Gardner[11] noted hyperlipemia in patients with high blood sugar values complicating acute pancreatitis. The lipemia disappeared with insulin therapy. The author has observed five instances of milky serum in pancreatitis. In three of the patients, no evidence of disturbed carbohydrate metabolism was noted nor was there a history compatible with idiopathic hyperlipemia. Careful laboratory study of the lipid problem was not carried out.

Fat embolism arising from the areas of fat necrosis may contribute to a fatal outcome in the disease.[8] In such circumstances fat stains of the lungs should be part of the histological study.

Hypopotassemia often occurs in the first 48 hours in severe pancreatitis.[8] Unless treated it does not return to normal until the patient is taking food by mouth. Several factors may contribute to the low serum potassium. The alarm reactions and loss by nasogastric suction are to be considered.

In severe necrotizing pancreatitis damage to the islets may produce diabetes mellitus,[27] even of such severity that acidosis supervenes. This possibility should not be overlooked as insulin therapy may prevent death.

CHRONIC PANCREATITIS

Recurrent attacks of acute pancreatitis often lead to chronic changes in the gland, but this is not invariably so. Occasionally a patient may have repeated attacks over many years and yet none of the characteristic symptoms of chronic relapsing pancreatitis intervene.

Early in chronic pancreatitis the amylase content of the blood may remain consistently elevated. Once fibrosis and atrophy have occurred in the pancreas, recurrent acute attacks may not be accompanied by such high serum amylase values as those ordinarily observed. Pseudocysts are common in chronic relapsing pancreatitis and may also cause persistently high amylase levels.

The more common physiological abnormalities in chronic pancreatitis are owing to the failure of the external secretion to enter the intestine in sufficient quantity to digest fats and proteins; steatorrhea and creatorrhea result. Contrary to the usual statement, failure of the internal secretion may occur fairly early in the course of the disease and diabetes mellitus will be the presenting symptom or the first complication noted after one or more attacks.[9] Glucose tolerance tests should be repeatedly done in patients with chronic relapsing pancreatitis.

The precipitation of calcium carbonate in the pancreatic juice to form calculi in the ducts and acini of the pancreas is another common complication. This, the author believes, is caused by the supersaturation of the juice with calcium and carbonate.[10] The demonstration of calculi by roentgenograms gives positive proof of chronic pancreatitis. In recent years, the author has noted calculi particularly in chronic alcoholics with pancreatitis which is often associated with cirrhosis.

Since the work of Agren and Lagerlof,[1, 2] many efforts have been made to measure the amount and concentration of enzymes in the external secretion as a guide to the progress of chronic pancreatitis.[19, 5, 21] Secretin, Mecholyl® or Urecholine® have been used to stimulate secretion. These methods require a tube with a double lumen, one for the duodenum and one for the stomach. This test is time-consuming and difficult for the patient, but valuable information can be gained from it.

Several investigators[16, 29, 12] have tried to arrive at the same conclusion by giving the patient a pancreatic stimulant and measuring the rise in serum amylase. There is a difference of opinion as to how helpful the results may be to the clinician. It seems safe to say that further investigation is necessary before a simple and highly diagnostic test for pancreatic function is evolved.

CARCINOMA OF THE PANCREAS

Physiological changes that aid in the diagnosis of cancer of the pancreas are few and vary with the location and extent of the tumor. Cancer of the tail of the pancreas usually does not affect the external or internal secretion. Cancer of the body of the gland may obstruct the duct of Wirsung or destroy extensively the secreting tissue. The same is true of cancer of the head of the pancreas, and in addition obstruction of the common duct occurs.

Fewer than half of the patients have increased content of amylase and lipase in the blood. If there is extensive destruction, diabetes may occur.

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Function tests using secretin, Mecholyl or Urecholine or some combination thereof have been attempted in the same manner as in the diagnosis of chronic pancreatitis. The most valuable test seems to be determination of the response of the external secretion to secretin given intravenously. Dreiling,[7] using this test, noted there was a decreased volume of juice in a high percentage of patients with cancer of the head and/or body of the pancreas. Cancer of the body with great destruction caused a pronounced decrease in the concentration of amylase and bicarbonate as well as small volume.

The serum secretin test,[16, 29] in which the amount of amylase in the blood is determined before and after injection of secretin, resulted most often in a failure of the amylase to rise. However, in some patients, presumably those with obstruction near the head of the pancreas, the serum amylase increased sharply.

Duodenal drainage has an advantage over the serum secretin test in that the bile pigments can be studied at the same time. Because secretin is an efficient cholagogue, the gallbladder empties. Thus, in jaundiced patients a normal flow of pancreatic juice in the absence of any biliary pigment would place the obstructive lesion in the biliary tract.

The early diagnosis of cancer of the pancreas remains a difficult problem that awaits more discerning methods.

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