California Association for Medical Laboratory Technology

Distance Learning Program

PATTY PANCREAS:
EXOCRINE FUNCTIONS AND DISORDERS

Course # DL-956

by
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Sacramento, CA

Approved for 2.0 CE
CAMLT is approved by the California Department of Public Health
as a CA CLS Accrediting Agency (#21)

Level of Difficulty: Intermediate

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DISTANCE LEARNING ANSWER SHEET
Please circle the one best answer for each question.

COURSE NAME: **PATTY PANCREAS**

NAME ________________________ LIC. # _______________ DATE ____________

SIGNATURE (REQUIRED) ____________________________________________________________

EMAIL _____________________________________________________________________________

ADDRESS __________________________________________________________________________

STREET      CITY    STATE/ZIP

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PAYMENT METHOD: [  ] CHECK OR [  ] CREDIT CARD # ______________________ TYPE – VISA or MC

EXP. DATE ________  |  SECURITY CODE: ___  -  ___  - ___

1. a b c d
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7. a b c d
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10. a b c d
11. a b c d
12. a b c d
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DISTANCE LEARNING EVALUATION FORM
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1. Overall, I was satisfied with the quality of this Distance Learning course.
   5 4 3 2 1
2. The objectives of this Distance Learning course were met.
   5 4 3 2 1
3. The difficulty of this Distance Learning course was consistent with the number of CE hours.
   5 4 3 2 1
4. I will use what I learned from this Distance Learning course.
   5 4 3 2 1
5. The time to complete this Distance Learning course was: __________ hours
5. __________
6. Please comment on this Distance Learning course on the back of this sheet. What did you like or dislike?
PATTY PANCREAS: EXOCRINE FUNCTIONS AND DISORDERS

Course Number: DL-956
2.0 C.E.
Level of Difficulty: Intermediate

Martha Kunkel, CLS
UC Davis Medical Center, Sacramento, Retired

ABSTRACT
The pancreas is made up of two types of glands: exocrine, which secrete digestive enzymes, and endocrine, which consists of the islets of Langerhans and secrete insulin and glucagon. This course will cover the exocrine functions including a general review of the physiology/pathophysiology of the pancreas. Three case histories will be presented representing each of the major exocrine dysfunctions of the pancreas: acute pancreatitis, chronic pancreatitis, and pancreatic carcinoma.

OBJECTIVES
After completing this course the participant will be able to:
1. outline the major exocrine functions and physiology of each.
2. explain the role of trypsin in the development of acute pancreatitis.
3. explain the laboratory values found with each pancreatic disease entity and the pathophysiology.
4. list the most common causes of acute and chronic pancreatitis.
5. discuss the use of cancer markers in the diagnosis of pancreatic cancer.

INTRODUCTION
According to Mosby Medical Encyclopedia, “The pancreas is a fish-shaped, grayish-pink gland about 5 inches long that stretches across the back of the abdomen, behind the stomach. It releases insulin, glucagon, and some enzymes of digestion. With a lumpy surface, the pancreas is divided into a head, a body, and a tail. Small ducts from the releasing cells empty into the main duct that runs the length of the organ (duct of Wirsung). The main duct empties into the intestine at the same spot as the exit of the common bile duct. About 1 million cell units (islands of Langerhans) are buried in the pancreas. Beta cells of the islands release insulin, which helps control the body’s use of carbohydrate. Alpha cells of the islands release glucagon, which counters the action of insulin. Other units (acinar cells) of the pancreas release enzymes that help digest fats and proteins.”

Disorders of the pancreas can be divided into two major groups, disorders involving the exocrine system (release of enzymes) and disorders involving the endocrine system (insulin production). The exocrine functions primarily affect the digestion of food and its absorption in the intestine. The endocrine pancreas is primarily involved with the production of insulin and the metabolism of glucose. This course will focus on the exocrine functions.

The exocrine portion of the pancreas contains clusters of acini or lobules. The acinar cells contain zymogen granules, which contain digestive enzymes. These granules
are discharged as part of the pancreatic juice. The number of zymogen granules in the cells varies, with more being found during fasting and fewer after a meal. The acinar cells secrete pancreatic juice into the duodenum through the pancreatic ducts in response to the hormones secretin and cholecystokinin (CCK) found in the enteroendocrine cells of the duodenum. Gastric acid and protein digestion products found in the duodenum cause the hormone secretin to be released. Cholecystokinin hormone is released when fat digestion and protein digestion products are present.

The pancreatic juice is made up of ions, water, and proteins. Approximately 1,500 ml. of pancreatic juice is secreted each day in response to gastric acid and products of digestion. The proteins are primarily enzymes and proenzymes (zymogens) along with plasma proteins, mucoproteins, and trypsin inhibitors. These enzymes are involved in the digestion and absorption of carbohydrates, fats, and proteins. Some of the enzymes are secreted in the active form (amylase, deoxyribonuclease, lipase, and ribonuclease). Others are secreted in the inactive form (chymotrypsinogen, phospholipase A2, procarboxypeptidase, and trypsinogen).

The proenzyme trypsinogen is changed to the active form trypsin by the enzyme enteropeptidase found in the duodenum. Trypsin then activates the other proenzymes. Trypsin also has the ability to activate trypsinogen, which can cause a self-perpetuating cycle. For this reason pancreatic juice contains a trypsin inhibitor to reduce the possibility of initiation of this self-perpetuating cycle.

The ions found in pancreatic juice are primarily HCO₃⁻, Cl⁻, Na⁺, and K⁺. Bicarbonate plays a significant role in controlling the pH of the digesting food and gastric acids (chyme) entering the duodenum from the stomach. A pH of 8.3 is not uncommon for the chyme entering the duodenum. In response to secretin, the duct cells of the pancreas release a large volume of pancreatic juice containing largely bicarbonate, as much as 150 meq/L HCO₃⁻, and very few enzymes. The bicarbonate acts to neutralize the chyme. When cholecystokinin (CCK) is released, the composition of pancreatic juice becomes high in enzymes and proenzymes and low in bicarbonate. With the chyme neutralized by the bicarbonate, the enzymes have a pH neutral environment in which to cleave peptide bonds and split straight-chain molecules into smaller alpha units as part of the digestive process. Thus carbohydrates, proteins, and fats are broken into maltose, free amino acids, fatty acids, lysolecithin, etc. that can then be absorbed in the intestines.

**CASE STUDY 1**

Patty Pancreas, a 48-year-old female, comes to the emergency department with acute abdominal pain radiating to the back. She has been sick for approximately 48 hours with flu-like symptoms or possibly food poisoning from a buffet. In the past few hours she has vomited several times with no relief from the pain; the pain actually seems to be increasing. Her husband stated that Patty takes a drink on special occasions and rarely drinks at any other time. She has never taken IV drugs. She has only been admitted to the hospital for childbirth and a gallbladder attack several years ago. She recovered without surgical intervention and has not experienced any problems since the original gallbladder attack. She indicated that she had eggs and bacon for breakfast, French fries and a hamburger for lunch, and fried chicken, corn, mashed potatoes and gravy for dinner and ice cream and homemade cookies for dessert.
Permission was obtained to perform drug testing, alcohol levels, and routine blood work (See Table 1). Patty was admitted to the Intensive Care unit with a diagnosis of Acute Pancreatitis. Upon admission her blood pressure (BP) was 140/72, pulse 68, respiration 24, and temperature 101.4 F.

<table>
<thead>
<tr>
<th>TEST</th>
<th>VALUE</th>
<th>Reference:</th>
<th>TEST</th>
<th>VALUE</th>
<th>Reference:</th>
</tr>
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<tbody>
<tr>
<td>Na+</td>
<td>141</td>
<td>135-145 mEq/L</td>
<td>WBC</td>
<td>11.0</td>
<td>4.5-11.0 K/mm3</td>
</tr>
<tr>
<td>K+</td>
<td>5.3</td>
<td>3.3-5.0 mEq/L</td>
<td>RBC</td>
<td>4.6</td>
<td>4.0-5.2 M/mm3</td>
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<tr>
<td>Glucose</td>
<td>266</td>
<td>95-110 mEq/L</td>
<td>Hgb</td>
<td>12.3</td>
<td>12.0-16.0 gm/dL</td>
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<tr>
<td>Mg++</td>
<td>1.3</td>
<td>1.5-2.6 mg/dL</td>
<td>Hct</td>
<td>52%</td>
<td>36-46%</td>
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<tr>
<td>Ca++</td>
<td>7.3</td>
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<td></td>
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<tr>
<td>Albumin</td>
<td>2.4</td>
<td>3.4-4.8 g/dL</td>
<td>pH</td>
<td>7.35</td>
<td>7.35-7.45</td>
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<tr>
<td>Alk Phos</td>
<td>163</td>
<td>34-115 U/L</td>
<td>PCO2</td>
<td>33</td>
<td>35-45 mm Hg</td>
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<tr>
<td>AST</td>
<td>307</td>
<td>15-43 U/L</td>
<td>PO2</td>
<td>90</td>
<td>83-108 mm Hg</td>
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<tr>
<td>GTT</td>
<td>210</td>
<td>0-65 U/L</td>
<td>HCO3</td>
<td>25</td>
<td>20-28 mmol/L</td>
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<td>Amylase</td>
<td>519</td>
<td>60-160 U/L</td>
<td>Base excess</td>
<td>1</td>
<td>-2 to +2 mEq/L</td>
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<tr>
<td>Lipase</td>
<td>519</td>
<td>13-51 U/L</td>
<td>Sat O2</td>
<td>91%</td>
<td>95-100%</td>
</tr>
<tr>
<td>LDH</td>
<td>891</td>
<td>90-200 U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>21</td>
<td>8-22 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>310</td>
<td>35-160 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.3</td>
<td>0.3-1.3 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>Negative</td>
<td></td>
<td>Drug Screen</td>
<td>Negative</td>
<td></td>
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</table>

**Discussion:** Patty presented with physical and laboratory findings consistent with Acute Pancreatitis (see Table 1). Due to the location of the pancreas, the pain associated with acute and chronic pancreatitis is typically located in the upper-left abdominal quadrant and may radiate to the back or flank areas. Patty had severe, persistent, and penetrating abdominal pain radiating to the back. She experienced no relief from the pain even after vomiting but instead the pain seemed to be increasing. Vomiting without a decrease in pain is considered a hallmark symptom of acute pancreatitis. Her amylase was more than 3 times normal and her lipase values were markedly elevated. Finally, her food consumption just prior to the pain had a high fat content. The development of acute pancreatitis is often directly associated with consumption of alcohol or a large meal with fatty foods.

Although there are many causes of acute pancreatitis, the two most common are alcohol and gallbladder/biliary tract disease. Patty’s ethanol level was negative upon admission and her history did not indicate alcohol abuse. A review of her laboratory values indicates gallbladder disease. Her GGT, alkaline phosphatase, and triglycerides were significantly elevated, common findings with cholestasis. The total bilirubin is above normal and the triggering event appears to be consumption of a diet high in fats.
An ultrasound shows a large number of gallstones present. The probable etiology of acute pancreatitis for Patty is gallbladder disease.

CASE 1 – Day 2

Patty was immediately started on normal saline IV with potassium, magnesium, and medications to control the pain. A nasogastic tube was inserted and she was made NPO (nothing by mouth). Blood cultures times 3 were drawn and Gentamicin was given every 8 hours after blood cultures had been collected. Daily complete metabolic panel, amylase, lipase, CBC, and ABG (arterial blood gasses) were ordered (See Table 2 for day 2 laboratory results).

<table>
<thead>
<tr>
<th>TEST</th>
<th>VALUE</th>
<th>Reference:</th>
<th>TEST</th>
<th>VALUE</th>
<th>Reference:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>139</td>
<td>135-145 mEq/L</td>
<td>WBC</td>
<td>14.6</td>
<td>4.5-11.0 K/mm³</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.2</td>
<td>3.3-5.0 mEq/L</td>
<td>RBC</td>
<td>3.82</td>
<td>4.0-5.2 M/mm³</td>
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<tr>
<td>Glucose</td>
<td>203</td>
<td>95-110 mEq/L</td>
<td>Hgb</td>
<td>10.3</td>
<td>12.0-16.0 g/dL</td>
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<tr>
<td>Mg₂⁺</td>
<td>1.1</td>
<td>1.5-2.6 mg/dL</td>
<td>Hct</td>
<td>42</td>
<td>36-46%</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>7.8</td>
<td>8.6-10.5 mg/dL</td>
<td>pH</td>
<td>7.22</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>Total Protein</td>
<td>4.6</td>
<td>6.3-8.3 g/dL</td>
<td>PCO2</td>
<td>26</td>
<td>35-45</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.2</td>
<td>3.4-4.8 g/dL</td>
<td>PO2</td>
<td>84</td>
<td>83-108</td>
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<tr>
<td>Alk Phos</td>
<td>179</td>
<td>35-115 U/L</td>
<td>HCO3</td>
<td>10</td>
<td>20-28</td>
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<tr>
<td>Amylase</td>
<td>575</td>
<td>60-160 U/L</td>
<td>Base excess</td>
<td>6</td>
<td>-2 to +2</td>
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<tr>
<td>AST</td>
<td>364</td>
<td>15-43 U/L</td>
<td>Sat O2</td>
<td>80%</td>
<td>95-100%</td>
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<tr>
<td>Lipase</td>
<td>789</td>
<td>13-51 U/L</td>
<td>LDH</td>
<td>798</td>
<td>90-200 U/L</td>
</tr>
<tr>
<td>LDH</td>
<td>798</td>
<td>90-200 U/L</td>
<td>Urea Nitrogen</td>
<td>14</td>
<td>8-22 mg/dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>245</td>
<td>35-160 mg/dL</td>
<td>Blood Cultures</td>
<td>Negative</td>
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</tr>
</tbody>
</table>

**Discussion**: Acute Pancreatitis is the most common exocrine dysfunction. Dysfunction of the exocrine pancreas results from inflammation (acute pancreatitis, chronic pancreatitis), carcinoma, duct obstruction by stones, or abnormally viscid mucus (cystic fibrosis). There are approximately 120,000 cases of acute pancreatitis reported each year in the United States with about 20% of cases being reported as severe. Acute pancreatitis is listed as the 235th cause of death with 3,000–3,500 a year. Both acute and chronic forms of pancreatitis are more common in men and men are more likely to develop the severe form. Some people have more than one attack and recover completely after each attack with no lasting effects. Others have only one episode that is a severe, life-threatening illness with multiple organ involvement. Still others develop chronic conditions that are never totally resolved. In addition to alcohol abuse and gallbladder disease, other possible causes of acute pancreatitis range from trauma, drugs, infections, metabolic, toxins, hereditary, biliary tract disease, and idiopathic. Although there are many causes, in the United States 50–65% of all cases are due to alcohol abuse. Approximately 50% of the remaining cases are attributed to gallbladder or biliary tract disease.
There have been many theories presented to explain what triggers an attack; however, there is still no universally accepted mechanism that explains the process involved for each cause. The outcome, however, is well documented. The pancreas becomes inflamed, with destructive autodigestion of the pancreas and variable involvement of other tissues or remote organs. Acute pancreatitis is believed to result from premature release of activated pancreatic enzymes that cause autodigestion, which leads to tissue injury, inflammation, necrosis, and sometimes infection. Trypsin is believed to be the enzyme that is initially activated that begins the autodigestion process by releasing chymotrypsin, phospholipase A, elastase, and kallikrein. The activation of chymotrypsin leads to edema and vascular damage. Elastase, once activated, digests the elastin in blood vessel walls causing vascular damage. The actual mechanism by which the enzymes become activated is still a major question. One theory is that there is hyperstimulation of pancreatic acinar cells similar to the mechanism seen with scorpion stings and insecticide poisoning. Another theory speculates that obstruction, bile reflux, and/or duodenal reflex disturb pancreatic acinar cell function, causing intracellular activation of the trypsin enzyme.

The severity of the disease varies and the prognosis ranges from mild, self-limited to death. There are several prognostic systems (1) (Ranson, Imrie, Blamey, Apache II, and Altanta) for predicting which patients will develop the more severe forms but each system has limited ability to successfully predict the outcome. Ranson’s criteria (Table 3) and the Apache II criteria are the most commonly used systems to evaluate adults. A separate system has been proposed by DeBanto, et al. (2) to evaluate children (Table 4).

<table>
<thead>
<tr>
<th>TABLE 3. RANSON’S CRITERIA*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria Present at diagnosis</strong></td>
</tr>
<tr>
<td>Age over 55</td>
</tr>
<tr>
<td>WBC &gt;16,000/ul</td>
</tr>
<tr>
<td>Blood glucose &gt;200 mg/dL</td>
</tr>
<tr>
<td>Serum LDH &gt;350 IU/L</td>
</tr>
<tr>
<td>AST &gt; 250 IU/L</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Mortality rates correlate with number of criteria present

<table>
<thead>
<tr>
<th>Number of criteria</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 2</td>
<td>1%</td>
</tr>
<tr>
<td>3 – 4</td>
<td>16%</td>
</tr>
<tr>
<td>5 – 6</td>
<td>40%</td>
</tr>
<tr>
<td>7 – 8</td>
<td>100%</td>
</tr>
<tr>
<td>Criteria at admission</td>
<td>Criteria at 48 hours</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>&lt; 7 years of age</td>
<td>Calcium &lt;8.3 mg/dL</td>
</tr>
<tr>
<td>&lt;23 kg weight</td>
<td>Albumin &gt;2.6 mg/dL</td>
</tr>
<tr>
<td>WBC &gt; 18,500</td>
<td>BUN &gt;5 mg/dL rise</td>
</tr>
<tr>
<td>LDH &gt;2000</td>
<td>Est. fluid sequestration &gt;75mL/kg/48hr</td>
</tr>
</tbody>
</table>

*3 criteria or more indicates those patients at risk for severe pancreatitis

A great amount of effort has been concentrated to find a test that has predictive value. However, there is no single test to date that can identify those patients who are at greater risk of developing the more severe form of acute pancreatitis. A study by Lempinen, et al. (3) compared urinary trypsinogen-2 with urinary trypsinogen activation peptide (TAP) and serum C-reactive protein (CRP) as possible early determinants of mild vs. severe disease. They concluded that urinary trypsinogen-2 was superior to serum CRP and as good as urinary TAP. A dipstick test for trypsinogen-2 is available. The addition of urinary trypsinogen-2 may be a valuable adjunct to the acute pancreatitis work up in the future. A test for trypsinogen-3 to diagnose acute pancreatitis has recently been studied and shows promise (Clin Chem 57-11, Nov 2011).

In another study reported in the World Journal of Gastroenterology (4), the role of oxygen free radicals was examined. This study concluded that oxygen-derived free radicals may be closely associated with the inflammatory process. The role of proinflammatory cytokines and oxidative stress is not completely understood. Serum levels of proinflammatory cytokines, such as TNF-alpha and IL-beta, are increased during the course of pancreatitis and appear to be the driving force for the initiation of the systemic response. In addition, Interleukin-6 and Interleukin-8 levels appear to be correlated with severity of the inflammation. The role of oxidative stress has been evidenced indirectly by observing the beneficial effects of antioxidants as well as directly by pancreatic glutathione depletion and increased lipid peroxidation. The determination of the plasma level of lipid peroxide (LPO) to measure the oxygen-derived free radicals may prove to be a meaningful index for determining the severity of the disease.

Currently, the primary laboratory finding in acute pancreatitis is the elevation of the serum amylase level, often 10–20 times normal with a three-fold increase being diagnostic. The amylase values are elevated within hours and concentrations return to normal 48-72 hours after onset even if symptoms are still present. Approximately 5–30% of patients will have normal or minimally elevated serum amylase levels. Since serum amylase is found in both the pancreas and salivary glands, amylase can also be elevated in a number of other disease processes. Patients with marked elevations of serum amylase, i.e. more than a 3-fold increase, usually have acute pancreatitis while those with lesser levels tend to have other conditions. Isoamylase P4 levels are more specific, but are generally performed by reference laboratories and not as readily available. Serum lipase levels are also elevated during the first 48-72 hours and remain elevated for 5-7 days. Lipase is found predominantly in the pancreas and decreases more slowly, making it a reliable diagnostic tool. Trypsin, elastase, and phospholipase A are also elevated but have
not been found to be any more reliable than amylase and lipase in diagnosis of acute pancreatitis and are more costly.

Laboratory studies and computed tomography (CT) are important in identifying the possible etiology of the event and then assisting in defining treatment and finally in predicting the outcome. Once the diagnosis is made, other laboratory studies are used to monitor response and provide treatment procedures. If we apply the laboratory values found on day one and day two for Patty against the Ranson’s criteria (Table 3), her statistical severity of disease can be assessed. Patty had a blood glucose >200, LDH >350, and AST >250 at admission. On day 2 she had Ca++ <8, and base excess >6. This gives her 5 out of 8 criteria, which translates to a 40% mortality rate using Ranson’s criteria.

**Blood Glucose >200 mg/dL:** Approximately 25% of patients have hyperglycemia and 10% have transient glycosuria. Blood glucose levels are elevated when the islets of Langerhans are affected with the resultant decrease in release of insulin. In patients with extensive pancreatic necrosis and hemorrhage, the decreased function of the islet cells can lead to acute diabetic ketoacidosis. In addition, increased levels of circulating catecholamines and glucocorticoids from the adrenal glands can result in elevated blood glucose levels.

**Ca++ <8 mg/dL:** Several factors contribute to the decline in serum calcium. Fat necrosis and release of free fatty acids occur when pancreatic lipase is released by damaged acinar cells and acts on the surrounding adipose tissue. The free fatty acids combine with calcium to form soaps. The parathyroid gland is unable to respond to the quick drop in calcium levels caused by the formation of soaps. A low level of magnesium exacerbates the problem, as magnesium is required for normal parathyroid function. Low albumin levels also contribute to lower calcium levels since about 50% of total blood calcium is protein-bound, predominantly to albumin. Thus, low values of albumin and total protein due to hypovolemia further act to decrease the amount of calcium present.

**Potassium:** In the initial phases of acute pancreatitis, acute inflammation and tissue necrosis cause release of large amounts of potassium into the circulation. This, combined with hypovolemia and possible acidosis, can result in hyperkalemia. Following fluid resuscitation and correction of acidosis, the potassium levels may fall to dangerous levels (hypokalemia).

**Prothrombin and Partial Thromboplastin Times:** Elevations of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) should be monitored for possible activation of the coagulation cascade due to tissue factor release during proteolysis. Purpura around the umbilicus (Cullen’s sign) or the flanks (Grey Turner’s sign) is seen with patients who develop disseminated intravascular coagulation with acute pancreatitis.

**Hematocrit:** A common complication associated with acute pancreatitis is hypovolemic shock. Hypovolemic shock commonly occurs as a result of fluid shifts from the vascular system to the intraperitoneal spaces (third spacing) as a result of the injury to the abdominal structures from the activated enzymes. Activation due to the acute inflammation of the proteolytic enzyme kallikrein results in peripheral vasodilation as a result of the liberation of the peptides bradykinin and kallidin. With the release of these kinins there is increased vasodilation and increased capillary permeability. As a result, large amounts of plasma and protein leave the vascular system with as much as 4 to 6 L
of fluid shifting into the abdomen. Cytokines, like platelet activating factor, a very potent vasodilator, and leukocyte activator have also been implicated in fluid shifting and development of shock. Patients who present at admission with a hematocrit of $>44$ are considered to be hemoconcentrated (5). Hemoconcentration relates to the amount of third spacing that has taken place. Aggressive replacement of fluids is essential in the prevention of hypovolemic shock. The failure of the hematocrit to drop in the first 24 hours predicts increased severity of disease and inadequate replacement of fluids.

**White Blood Cells:** Premature activation of pancreatic enzymes appears to be the major cause of acute pancreatitis; however, Banks suggests that the release of activated polymorphonuclear leukocytes and their secretions may have more to do with the severity of the disease than the release of activated enzymes.

CASE Study 1 – Day 6

Patty’s laboratory values have returned to normal and she is released from the hospital. A cholecystectomy is scheduled for five weeks after discharge.

**Discussion:** Most cases of acute pancreatitis can be treated with pain medication and intravenous fluids until the inflammation subsides. Antibiotics may be given as a prophylactic measure to prevent infection. The usefulness of antibiotics prior to confirmation of infection is debated. On occasion, surgery is required to remove a portion of the pancreas if the extent of damage caused by inflammation and infection has caused extensive necrosis.

Severe pancreatitis with systemic inflammatory response syndrome and multiple organ failure has a high incidence of mortality. At present there is no treatment for severe acute pancreatitis, other than supportive care.

CASE Study 1 – Day 18

Patty returns to the emergency room with vomiting, abdominal pain, and fever of 102.4. A CBC, complete metabolic panel, Magnesium, PT, and APTT are ordered. Her WBC count is elevated but all other values are within normal ranges. A CT scan is ordered.

**Discussion:** The CT shows a possible pancreatic pseudocyst or abscess. A CT guided needle aspiration is performed. Culture of the aspiration material grew out *Escherichia coli.* Antibiotics (6) are begun and the site is surgically drained. This relieves Patty’s symptoms and she has no further episodes.

Inflammatory pseudocysts are non-epithelium-lined cavities that contain pancreatic tissue and juice, debris, enzymes, pus, and blood. The infection usually presents 2 weeks after the initial symptoms. They are the result of ductal obstruction and necrotic tissue. Some acini cells continue to secrete pancreatic juice, but due to the obstruction cannot drain. Therefore pancreatic juice and debris collect, forming the pseudocyst. If pancreatic juice continues to be secreted, the cyst may become large enough to compromise surrounding structures such as the portal vein, common bile duct, bowel, or may even rupture leading to hemorrhagic shock. Pseudocysts generally resolve without surgical treatment but close monitoring with CT scans or MRI is critical to prevent possible complications.

Pancreatic abscesses generally form 4–5 weeks after an episode and are the result of necrotic tissue that is infected by gastrointestinal bacteria such as *Escherichia coli,*
Pseudomonas, Staphylococcus, or Klebsiella. Abscesses typically require surgical intervention and antibiotic therapy.

CASE STUDY 2

Patty Pancreas had a cholecystectomy 3 months after the initial acute pancreatitis episode. During her yearly physical she tells her physician that she continues to experience intermittent episodes of low level pain that seems to be worse after eating. She also reported that she has dropped 35 pounds without trying. Her physician notes that she appears to be somewhat jaundiced. Laboratory studies and CT scan are ordered (see Table 5). The CT scan showed calcifications and dilated pancreatic ducts.

<table>
<thead>
<tr>
<th>TEST</th>
<th>VALUE</th>
<th>Reference:</th>
<th>TEST</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>139</td>
<td>135-145 mEq/L</td>
<td>WBC</td>
<td>10.1</td>
<td>4.5-11.0 K/mm³</td>
</tr>
<tr>
<td>K⁺</td>
<td>3.6</td>
<td>3.3-5.0 mEq/L</td>
<td>RBC</td>
<td>4.0</td>
<td>4.0-5.2 M/mm³</td>
</tr>
<tr>
<td>Glucose</td>
<td>128</td>
<td>95-110 mEq/L</td>
<td>Hgb</td>
<td>11.5</td>
<td>12.0-16.0 g/dL</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>103</td>
<td>95-108 mEq/L</td>
<td>Hct</td>
<td>36</td>
<td>36-46%</td>
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<tr>
<td>Ca²⁺</td>
<td>8.6</td>
<td>8.6-10.5 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Protein</td>
<td>6.3</td>
<td>6.3-8.3 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2</td>
<td>3.4-4.8 g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk Phos</td>
<td>122</td>
<td>35-115 U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirub</td>
<td>1.9</td>
<td>0.3-1.3 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>40</td>
<td>15-43 U/L</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amylase</td>
<td>205</td>
<td>60-160 U/L</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lipase</td>
<td>79</td>
<td>13-51 U/L</td>
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<td></td>
</tr>
<tr>
<td>LDH</td>
<td>230</td>
<td>90-200 U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>11</td>
<td>8-22 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>175</td>
<td>35-160 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion: Typically, chronic pancreatitis presents with intermittent or constant pain (7). However, between 10% and 20% experience no pain, and present with diabetes, jaundice, malabsorption, anorexia, and weight loss only. Patty has lost weight and her total bilirubin is up along with slightly decreased albumin and potassium levels. Her glucose is increased, suggestive of diabetes. A CT scan showing calcifications is highly suggestive of chronic disease; however, a pancreatic biopsy is needed to confirm the diagnosis. Although there is an ongoing debate about the relationship between gallstones and chronic pancreatitis, in one series gallstones were the only finding in 17 of 462 patients with chronic pancreatitis.

Chronic pancreatitis is a poorly understood disease with various clinical presentations. At one time it was believed that the chronic form of pancreatitis resulted from recurrent acute attacks. This now appears to be true in some cases but not all. On average patients with chronic pancreatitis are 13 years younger at onset of symptoms than are most patients experiencing an initial attack of acute pancreatitis. Thus repeated acute episodes do not appear to be the trigger for most cases of chronic pancreatitis. Another
major difference between acute and chronic is that with an acute attack, the pancreas is normal before the attack and the changes are completely reversible after the attack. However in chronic pancreatitis, the pancreas is abnormal before the attack and the changes are permanent. Previously chronic pancreatitis was thought to have a prevalence of 30 per 100,000 individuals. The utilization of new molecular and genomic technologies and progress in pancreatic imaging techniques has resulted in estimates of an overall prevalence rate of 45.4 per 100,000 in males and 12.4 per 100,000 females and these figures appear to be increasing.

The etiology and risk factors for chronic pancreatitis can be categorized into five major groups: toxic-metabolic, idiopathic, genetic, autoimmune, and obstructive. The majority of patients with chronic pancreatitis fall into the toxic-metabolic group. The major cause within this group is chronic alcoholism, which accounts for 70-80% of cases in the United States. The first reported case tying alcohol with chronic pancreatitis was in 1788 when a young man with a drinking problem was discovered to have a pancreas “full of stones” at autopsy. Alcohol use precedes disease in 55%-80% of patients. The onset appears to occur after a long history of alcohol abuse (6-12 years) and consuming large quantities of alcohol (150-175 g/day). Although the risk of chronic pancreatitis increases as a function of the quantity of alcohol consumed, there is no apparent threshold of toxicity. Alcohol appears to be a cofactor rather than the primary factor. Two clinically different pain patterns are found with alcoholic pancreatitis. The first (A type) is characterized by short relapsing pain episodes separated by pain-free episodes. The second (B type) is characterized by prolonged periods of either persistent pain or clusters of recurrent severe pain.

The role of genetic factors still needs to be evaluated, but advances in genetics have provided new insight into chronic pancreatitis (8). Hereditary pancreatitis is responsible for 2-3% of all cases of chronic pancreatitis. Patients with hereditary pancreatitis often present at an early age and have a 50-60% increased risk of developing pancreatic cancer.

Trypsinogen plays a central role in activation of other proenzymes in the digestive process. Premature activation of trypsinogen in the pancreas is thought to lead to pancreatic autodigestion. Two mechanisms are present to prevent the premature release of the active form trypsin: trypsin inhibitor and trypsin autolysis.

1. Trypsin inhibitor: trypsinogen and SPINK1 (also known as pancreatic secretory trypsin inhibitor PSTI) are produced by the acinar cells at a 5 to 1 ratio. If trypsinogen is activated in the acinar cells, the SPINK1 inhibits up to 20% of trypsin. If excessive trypsin is present, the trypsin inhibitor will not be sufficient to prevent trypsin from activating the proenzymes. Free trypsin activity, again, increases and threatens to initiate the activation cascade.
2. Trypsin autolysis: autolysis cleaves the side chain connecting the 2 halves of the trypsin molecule. In autosomal dominant hereditary pancreatitis, mutation of the trypsinogen gene at codons 29 and 122 results in a substitution that prevents the autolysis mechanism. Mutations of SPINK1 do not appear to cause hereditary pancreatitis but seem to act in conjunction with other genetic and/or environmental factors to predispose the patient to pancreatitis.

The diagnosis of chronic pancreatitis is based on pancreatic biopsy. Computed tomography, endoscopic retrograde pancreatography, endoscopic ultrasonography, and
magnetic resonance imaging provide the best tools for staging and follow up. Laboratory studies are used to assess the degree of malabsorption and to direct supportive therapy.

**CASE STUDY 3**

Patty is now 58 years old and continues to have follow-up examinations with her physician. She takes pancreatic enzymes to enhance digestion and has been pain free for the past 3 years. Lately she has noticed that she is again having problems with weight loss and has been extremely tired and weak. She also noted that her eyes appear to be somewhat yellow. Laboratory studies (Table 6) and a CT scan of the pancreas are ordered.

<table>
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<tr>
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<td>RBC</td>
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<td>Glucose</td>
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<td>Hct</td>
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<td>36-46%</td>
</tr>
<tr>
<td>Ca++</td>
<td>9.1</td>
<td>8.6-10.5 mg/dL</td>
<td>Total Protein</td>
<td>6.2</td>
<td>6.3-8.3 g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0</td>
<td>3.4-4.8 g/dL</td>
<td>Alk Phos</td>
<td>195</td>
<td>35-115 U/L</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>2.5</td>
<td>0.3-1.3 mg/dL</td>
<td>AST</td>
<td>76</td>
<td>15-43 U/L</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>175</td>
<td>60-160 Units</td>
<td>Lipase</td>
<td>64</td>
<td>13-51 U/L</td>
</tr>
<tr>
<td>LDH</td>
<td>400</td>
<td>90-200 U/L</td>
<td>Urea Nitrogen</td>
<td>11</td>
<td>8-22 mg/dL</td>
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<td>Triglyceride</td>
<td>205</td>
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**Discussion:** Over 45,000 new cases of pancreatic cancer are diagnosed each year in the United States. The rates have been slowly increasing over the past 10 years. It is the fourth leading cause of cancer death and accounts for 5% of cancer deaths in the U.S. Pancreatic carcinoma usually presents after the age of 50 and increases in incidence with age. Long standing alcohol-related chronic pancreatitis increases the risk of developing pancreatic cancer by 50-60%. The disease is six times more common in diabetic women than non-diabetic women. However, this does not apply to diabetic men, who appear to have a normal pattern of incidence. Cigarette smokers have a 2-5 times greater chance of developing pancreatic cancer than non-smokers. Hereditary pancreatitis patients account for a small percentage of the total cases but have a 5-6 fold risk of developing pancreatic cancer with 40-50% of patients developing pancreatic cancer by the age of 70. With the exception of islet cell carcinoma, pancreatic cancer is rarely curable. The 5-year survival rate is only about 6%.

The clinical presentation of pancreatic cancer is often indistinguishable from chronic pancreatitis. Both the location of the tumor and the histological type influence the
presenting symptoms. Patients with tumors of the body or tail of the pancreas usually present with abdominal pain, weight loss, anemia, and abdominal mass. These patients usually present at later stages and more often have metastases, particularly to the liver. Patients with tumors of the head of the pancreas present with painless and progressive jaundice. This is thought to be due to the obstruction of the common bile duct.

A variety of tumor makers, such as CEA, CA 19-9, and CA 242 can be found in the serum of patients with pancreatic cancer. In a study by Ozkan, et al. (9), 135 subjects with pancreatic cancer, other cancers (cholangiocellular, hepatocellular), chronic and acute pancreatitis, and normal subjects were tested for CA 242, CA 19-9 and CEA. Mean serum CA 242, CA 19-9 and CEA levels were significantly higher with the pancreatic cancer group than the other groups with the exception of cholangiocellular carcinoma. No significant difference existed between the stages of pancreatic cancer and the cancer marker levels. CA 242 had a higher specificity (85.5%) than CA 19-9 (67.3%) and CA 242 was slightly less sensitive (75%) than CA 19-9 (80%) in the diagnosis of pancreatic cancer. Amylase and lipase do not appear to provide any additional diagnostic information. Alkaline phosphatase, LDH, and AST are elevated in 60-70% of the patients and albumin is decreased in approximately 55-65% of the patients.

DNA flow cytometry and nuclear morphometric analysis of the mitotic rate have been useful in staging and prognosis. Approximately 25% of the patients have diploid tumors. DNA diploid tumors appear to be less aggressive and surgically resectable. The remaining tumors are either tetraploid or aneuploid with survival rates of 5 and 4 months respectively. Only about 10% of pancreatic tumors are diagnosed early enough for successful surgical resection. In a large retrospective review of 37,000 cases, 4,100 patients had surgical intervention and out of that number only 156 patients were long term survivors. In this review the overall survival rate was only 0.4%.

SUMMARY

Pancreatic disorders of the exocrine functions result in 3,000 to 3,500 deaths a year from both pancreatic carcinoma and acute pancreatic episodes. The number of cases is increasing dramatically but the reason is obscure. The advances in genetics have provided some insights into the mechanism, but triggers leading to pancreatic dysfunction are still poorly understood. Rapid recognition is vital to limit the severity of disease process. Laboratory and radiological studies along with clinical presentation are essential in the early diagnosis of acute pancreatitis. Amylase and lipase continue to be simple tests of choice for diagnosis. Predicting severity of the disease process continues to be problematic with no single factor being an indicator. Continued research will be required to find the mechanism(s) and reduce the mortality of pancreatic disease.
REFERENCES

Review Questions
Course #DL-956
Choose the one best answer

1. The cells responsible for generation of pancreatic juice are
   a. beta cells
   b. acinar cells
   c. enteroendocrine cells
   d. islet cells

2. Zymogen granules contain
   a. digestive enzymes
   b. gastrin
   c. secretin
   d. cholecystokinin

3. Secretin is released in response to
   a. fat digestion products
   b. bicarbonate
   c. phosphate
   d. gastric acid

4. Cholecystokinin (CCK) triggers release of pancreatic juice rich in
   a. bicarbonate
   b. trypsinogen
   c. enzymes
   d. phospholipase C

5. The two most common causes of acute pancreatitis are
   a. trauma and hereditary pancreatitis
   b. drugs and infections
   c. alcohol and gallbladder disease
   d. poisons and toxins

6. According to the article, advantages of lipase as a reliable diagnostic tool for acute pancreatitis include all but which of the following?
   a. Values are elevated within 48-72 hours
   b. Values stay high for 5-7 days
   c. Lipase is found predominately in the pancreas
   d. PCR testing increases the sensitivity

7. To be diagnostic for acute pancreatitis, amylase levels must be
   a. over 20 times reference range
   b. over 10 times reference range
   c. over 3 times reference range
   d. 2 times reference range
8. Acute Pancreatitis is believed to result from premature release of
   a. trypsin
   b. amylase
   c. elastase
   d. kallikrein

9. The two most common prognostic systems used to predict severity of disease are
   a. Apache II and Altanta
   b. Ranson and Imrie
   c. Blamey and Altanta
   d. Ranson and Apache II

10. A possible test procedure to determine mild vs. severe disease is
    a. urinary trypsinogen-2
    b. urinary trypsinogen activation
    c. serum C-reactive protein
    d. phospholipase A2

11. Blood glucose values rise in pancreatitis due to
    a. effect of elastase on vascular walls
    b. damage to islets of Langerhans
    c. decreased levels of glucocorticoids
    d. increased levels of IL-6 and IL-8

12. Lipase released as a result of pancreatic acinar cell damage acts on
    a. vessel walls
    b. muscle tissue
    c. endothelial cells
    d. adipose tissue

13. Pseudocysts are a result of
    a. activated enzymes
    b. high levels of bicarbonate
    c. pancreatic juice and debris
    d. digestive products

14. Chronic pancreatitis is more commonly found in
    a. men
    b. women
    c. individuals with a normal pancreas before an acute attack
    d. men and women > 60 years of age
15. Hereditary pancreatitis accounts for what percent of chronic pancreatitis cases?
   a. 70-80 %
   b. 4-5 %
   c. 50-60 %
   d. 2-3 %

16. Pancreatic secretory trypsin inhibitor inhibits up to ___% of active trypsin.
   a. 10
   b. 20
   c. 30
   d. 40

17. In autosomal dominant hereditary pancreatitis mutation of the trypsinogen gene at codon 122 results in a substitution which prevents
   a. autolysis
   b. inhibition
   c. digestion
   d. dilation

18. Patients with hereditary pancreatitis have a ___ fold increased risk of developing pancreatic cancer.
   a. 2
   b. 3
   c. 4
   d. 5

19. In pancreatic cancer, cancer marker CA 242 had
   a. the same specificity as CA 19-9.
   b. the same sensitivity as CA 19-9.
   c. higher specificity than CA 19-9.
   d. higher sensitivity than CA 19-9.

20. Pancreatic tumors that are diploid
   a. are more aggressive
   b. are surgically resectable
   c. have short survival rates
   d. are found early