CHRONIC RELAPSING PANCREATITIS

Report of 19 Cases

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Chronic relapsing pancreatitis, as described by Comfort, Gambill, and Baggenstoss,[1] is a distinct clinical entity representing a summation of repeated attacks of acute interstitial (edematous) pancreatitis, repeated sublethal attacks of acute necrotic pancreatitis, or a combination of the two types. Fibrosis or necrosis and atrophy are the constant chronic changes; pancreatic lithiasis, pseudocysts and cysts are less frequent evidence of chronic damage.

I. Etiology

From clinical survey, Morton[2] summarizes the five principal contributing causes of pancreatitis as follows:

1. Trauma, accidental or surgical.
2. Infections, with extension to the pancreas or biliary tract.
3. Toxic agents such as alcohol, drugs (arsphenamine), anesthetics.
4. Biliary obstructions such as stones, spasm, infection, tumor, and duodenal diverticulum.
5. Circulatory factors such as stasis, hypertensive apoplexy, thrombosis, and embolism.

Pediatricians find that pancreatitis may result from the presence of round worms in the pancreatic duct. They believe the most frequent cause to be hereditary syphilis. They also find that this disease accompanies gastroenteritis. Chronic pancreatitis is also seen in diabetes mellitus of childhood. Some cases of infantilism are believed to be associated with disturbances of the functions of the pancreas.[3]

Before recurrent pancreatic attacks were recognized as evidence of pancreatic degeneration, chronic disease of this gland was considered to be associated only with disorders of the parenchyma, as seen in carcinoma, inflammation caused by penetrating ulcers, pancreatic calculi, chronic disease of the liver or gallbladder, generalized arteriosclerosis, and benign or malignant occlusion of the pancreatic duct. Syphilis and alcoholism have been classed as primary etiologic factors, and some authors describe a pancreatic asthenia which follows operations on the biliary tract.

II. Pathology

Pathologically the three recognized forms of *acute* pancreatitis are acute hemorrhagic pancreatitis, suppurative pancreatitis, and gangrenous pancreatitis. Acute hemorrhagic and gangrenous pancreatitis are misnomers and should be classed simply as acute necrosis of the pancreas with or without hemorrhage.[4] Suppurative pancreatitis is considered a form of necrosis in which the clinical course and pathologic findings are less severe. Interstitial (edematous) pancreatitis is a less frequent pathologic finding, insofar as only swelling and edema of the gland are involved, consequently biopsy and necropsy material are not as plentiful. Perhaps this is a type of suppurative disturbance in which the etiologic agent is less virulent.

Chronic pancreatitis is characterized by an increase in stroma. The destruction becomes of clinical importance either when the ducts have become occluded or the glandular elements so destroyed that quantity or quality of pancreatic exocrine or endocrine secretion is affected.

In severe acute or acute exacerbation of pancreatitis the organ is large, soft, and friable. On the surface of the pancreas and the surrounding mesenteric fat may be seen small, white, opaque areas of fat necrosis. Frequently the abdominal cavity contains a serous or serohemorrhagic exudate which is not permanent. Dragstedt[5] believes that bacterial decomposition of proteins results in the poisonous material responsible for shock. The true cause of pancreatic death is still unknown.

Pancreatic lithiasis, usually in the major ducts, is ascribed to stasis in the duct system, infection, pancreatic metabolic disturbances, and mucous plugs in the ducts. Metabolic disturbance of the pancreas associated with formation of pancreatic calculi is difficult to appreciate, since calculi are composed of calcium phosphate salts with variable amounts of material of colloidal degeneration. Pancreatic secretion normally contains minimal amounts of these salts.

III. Clinical Features

Chronic pancreatitis has been a fairly frequent pathologic diagnosis at necropsy but a relatively rare clinical diagnosis. During life such a diagnosis has usually been limited to cases in which one or more of the major criteria of pancreatic lithiasis, diabetes, steatorrhea, and/or creatorrhea can be demonstrated.

At Cleveland Clinic we have studied 19 proved cases of primary chronic relapsing pancreatitis with no intercurrent or associated disease. Diagnoses were confirmed by surgical exploration in 10 cases, roentgenologic demonstration of pancreatic calculi as well as surgical exploration

in 4 cases, roentgenologic demonstration of pancreatic calculi in 3 additional cases, and by clinical studies alone in 2 cases.

Chronic relapsing pancreatitis is usually a disabling disease, frequently poorly managed. Seven of our patients were chronic users of codeine or morphine. During the course of their plight, patients with this disturbance are usually considered neurotics, and all of our 19 patients, at some time, were described as nervous or irritable and their symptoms were believed to be functional.

TABLE

Summary of Salient Features

1. **Cases:**
   - Males . . . 8
   - Females . . . 11
2. **Age:**
   - Below age 10 . . . 1
   - Age 10 to 20 . . . 0
   - Age 20 to 30 . . . 1
   - Age 30 to 40 . . . 5
   - Age 40 to 50 . . . 8
   - Age 50 to 60 . . . 4
3. **Duration of Symptoms to Diagnosis:**
   - One year or less . . . 7
   - One to two years . . . 6
   - More . . . 6
4. **Weight, in recent history:**
   - Decided loss . . . 8
   - Moderate loss . . . 5
   - Slight loss . . . 1
   - No change . . . 5
   - Gain . . . 0
5. **Diagnosis Confirmed by:**
   - Surgical exploration . . . 10
   - X-ray (calculi), surgical exploration . 4
   - X-ray (calculi), clinically . . . 3
   - Clinical studies only . . . 2
6. **Location of Pain:**
   - Epigastrium . . . 15
   - RUQ . . . 1
   - RUQ, Epigastrium . . . 1
   - RUQ, Abdomen . . . 1
   - Low Abdomen . . . 1
7. **Radiation of Pain:**
   - Back (low thoracic, high lumbar) . . . 5
   - Back, RUQ . . . 2
   - Back and Right Axilla . . . 1
   - Back and Left Shoulder . . . 1
   - Back and Right Scapula . . . 1
   - Back and lower quadrants . . . 1
   - LUQ, RUQ . . . 1
   - RUQ . . . 2
   - Right Shoulder . . . 2
   - Generalized Abdominal . . . 2
   - None . . . 1
8. **Relationship to Meals:**
   - None determined . . . 11
   - 0—30 minutes p.c. (not all foods) . . . 4
   - 1—3 hours p.c. . . . 2
   - Aggravated by eating; story indefinite 2
9. **Diarrhea in history:** (Sporadic or Chronic)
   - Yes . . . 7
   - No . . . 12
     - (Constipated . . . 6)
10. **Stools:**
    - Not unusual, normal type . . . 8
    - Loose, frothy, fats, soaps, fatty acids . 6
    - Foul, mucus . . . 1
    - Yellow-green, greasy. Examination neg . . . 3
    - Steatorrhea, creatorrhea . . . 1
11. **Nausea and Vomiting in history:**
    - Much . . . 10
    - Some . . . 4
    - Rare . . . 2
    - None . . . 3
12. **Diabetes during known history of patient:**
    - Yes . . . 5
    - No . . . 9
    - Transient . . . 5
13. **Amylase Test:** Tested Cases—10
    - Normal range . . . 6
    - Elevated . . . 4
14. **Lipase Test:** Tested Cases—4
    - Normal range . . . 3
    - Elevated . . . 1

The salient features of the study of our 19 cases are listed in the table. Our observations are consistent with those in the 29 cases reported by Comfort *et al.*,[1] the only discrepancy being in sex incidence. In our series 11 patients were women, as compared with 4 women of the 29 patients reported by Comfort *et al.* McClure and Jankelson[6] found pancreatitis twice as often in women as in men, and Gruber[7] found that 65 per cent of cases of acute necrosis occurred in women.

Pancreatic disease apparently occurs at an earlier age than does biliary disease. It has not been readily diagnosed unless the patient was seen during an attack or early convalescence. Surgical intervention and roentgenographic findings of pancreatic calculi have been responsible for the majority of diagnoses.

This entity is characterized by severe epigastric pain with radiation to the back, having vague or no relationship to meals, and sometimes a history of diarrhea. The incidence of chronic constipation is approximately the same as that of diarrhea. If diarrhea is present, the history of fat in the stool (steatorrhea), or undigested muscle fibers in the stool (creatorrhea) is helpful in clinching the diagnosis. These findings were present in 7 of our cases.

A survey of the literature and close study of our cases indicate that nausea, vomiting, and weight loss are pronounced. Diabetes develops in far-advanced cases and in many mild cases that affect the tail of the pancreas (the greater portion of diabetogenic cells being in the tail). Transient diabetes can be explained by postulating the presence of disturbed function due to edema and/or hemorrhage so that with healing the islet cells are again normal and can pursue normal activity.

During an attack or early convalescence, blood amylase and lipase levels show an elevation. This rise in level of the blood enzymes is ascribed to their inability to pass normally into the duodenum because of obstruction, edema, hemorrhage, and/or fat necrosis.

Three of our patients experienced attacks of jaundice (mild) at some time during the course of their disease. Only 2 patients could be proved abnormally alcoholic. In 1 the condition was associated with pancreatic calculi and in 1 with fatty infiltration of the liver. A third patient had lues.

IV. Diagnosis

A patient with pancreatic dysfunction should be subjected to thorough and critical examination. The clinical history should be carefully investigated, and an attempt to establish the major criteria of steatorrhea, diabetes, and pancreatic lithiasis should always be undertaken. Creatorrhea is pathognomonic of pancreatic disease.[6] An upper gastro-

intestinal roentgen survey should be undertaken, since characteristic deformity of the duodenum is occasionally present in pancreatic disturbance. Investigation of pancreatic function should be made by duodenal drainage and enzymatic activity studied. Findings indicative of low enzymatic activity are strong adjuncts in the diagnosis, however, interpretation of pancreatic function tests is difficult and probably not wholly reliable. Many biochemists believe that these function tests are of no particular clinical significance unless absolutely no enzymatic response can be found after stimulation of the pancreatic output, not only after one examination but after several. Comfort[8] indicates that there is normally a wide range in these enzyme levels; this range is so great that it in itself supports the idea that only negative results are of value.

Academically acute exacerbations of chronic relapsing pancreatitis should be differentiated from acute pancreatitis but practically there is little difference between acute necrotic or acute interstitial (edematous) pancreatitis and severe acute exacerbations of chronic pancreatic disease, for the edema, infiltration, rupture of ductules, hemorrhage, and necrosis that ensues in acute disease are also present in the acute exacerbation of the chronic disease.

As in acute pancreatitis, patients with severe acute exacerbation also demonstrate spasm and rigidity of the abdomen, may be seriously ill, and may also be in shock. The Gray-Turner sign[9] (mottled slate gray to brown discoloration of the abdomen and thighs) sometimes seen in acute pancreatitis is rarely seen in acute exacerbation.

Morton[2] believes that acute interstitial (edematous) pancreatitis can be diagnosed by function tests and by rapid improvement of the disease under conservative therapy but that pancreatic necrosis must be suspected if the patient fails to improve in a few days. This differentiation, considered difficult by most clinicians, is important to him, since he advises medical management in edematous pancreatitis and surgical intervention in the latter case.

Blood count, sedimentation rate, frequency of attacks, variation in appetite, gastric analysis, and temperature record have not been useful in making diagnoses.

If, in the investigation of the patient, other diseases are established, the presence of pancreatic disturbance must not be excluded on this basis. Secondary pancreatitis is also a part of the group entity of chronic relapsing pancreatitis and must be considered in any patient investigated for gastrointestinal disease.

As yet, no syndrome or true clinical signs have been established as resulting from pancreatic hypofunction indirectly following achylia

gastrica or achlorhydria. There is no evidence to show that hypersecretion of the pancreatic enzymes has any deleterious effect on the body. Occasionally osteomalacia occurs during the course of chronic pancreatic disease, but this has not been explained in any satisfactory manner.

Animal experiments indicate an increase in the alkaline serum phosphatase[10] and a definite reduction of prothrombin[11] in pancreatic disease.

V. Treatment

In an acute attack it may be difficult for the clinician to differentiate between acute edema and acute necrosis; because of this difficulty surgical intervention is usually the treatment of choice. Such surgical procedures include exploration, correction of biliary disease, relief of pressure on the duodenum with cholecystostomy and drainage, drainage of pancreatic cysts or abscesses, removal of calculi from pancreatic ducts, anastomosis of the gallbladder (if the cystic duct is patent) to the bowel, and drainage of the common bile duct. The last procedure is usually carried out in all operated cases of pancreatitis. Whipple[12] suggests that in the presence of normal gastric acidity cholecystogastrostomy or cholecystoduodenostomy are satisfactory procedures, but in the presence of achlorhydria cholecystojejunostomy is preferred. Partial or total pancreatectomy may be necessary in cases of intractable pain.

Besides drainage of the peritoneal and lesser peritoneal cavities, many surgeons advocate multiple incisions into the pancreas for drainage. There is some controversy on this subject, and Elman[13,14] states that in acute interstitial (edematous) pancreatitis the pancreas should never be incised. As a rule capsule rupture is usually unsatisfactory in any case.

Occasionally in recent years spinal anesthesia and sympathetic block anesthesia have been used to relieve the pain of acute or acute exacerbation of pancreatitis.

All patients with pancreatitis must be maintained on medical management thereafter, and all those with acute pancreatic disturbance must be considered as cases of impending pancreatic dysfunction. In all cases of pancreatic dyspepsia, prophylactic measures should be employed. These consist of proper treatment of diseases of the gallbladder, bile duct, and liver, and of management of ulcer, duodenitis, and gastritis, if present. Total abstinence from alcoholic beverages should always be observed. Substitution therapy should be employed, and, if on duodenal drainage only the amylase activity is decreased, taka diastase or a similar compound can be given with each meal; if other enzymes are

diminished in activity, total pancreatic replacement should be undertaken and the patient given raw, finely-ground pancreas, served with salt, in as large amounts as he can tolerate, or purified pancreatic extract with a minimum of 5 Gm. per meal but up to 20 Gm. per day if well tolerated. Purified nonprotein-containing pancreatic extract, available commercially for intramuscular administration, has not proved to be of value.

For achlorhydria or hypochlorhydria, hydrochloric acid should be added to the regimen; for hyperacidity, antacids should be recommended. In biliary dyskinesia, antispasmodics and sedatives should be administered to relieve spasm and irritation. In cases of irritable colon, bowel management should be undertaken. The values of carbohydrate, fat, and protein in the diet should be judged according to the degree of creatorrhea and steatorrhea and also according to the amount of enzymatic activity found by duodenal drainage. If any one enzyme be low in activity, the diet can be arranged to include a minimal intake of that particular substrate upon which the enzyme is active. Ordinarily, however, carbohydrates should constitute the major portion of the diet because they are the most easily assimilated. The protein requirement may be aided by feeding partially digested proteins and amino acids; the neurogenic influence through the vagus nerve can be somewhat stimulated by the feeding of peptone. The diet should always be bland; seeds, skins, coarse fibers, and condiments should be avoided. All high protein content foods must be cooked. Junket or gelatin is readily assimilated and so should be prescribed. If there is disturbance of the islet cells of Langerhans, the diabetes or hypoglycemia should be managed.

Because of the controversy over lipocaic and the influence of the pancreas on fatty degeneration of the liver and because of recent evidence that there are other fat metabolites in the pancreas, choline should also be included in the daily regimen. It should be taken at least with the two larger meals of the day. Adequate vitamin and mineral intake should be maintained and a healthy routine of life advised. The prothrombin time of the blood should be watched.

Roentgen therapy is not now considered a useful adjunct to management.

Prognosis is poor in severe acute pancreatitis and also in severe acute exacerbations of chronic pancreatic dysfunction. In a patient with chronic relapsing pancreatitis, whether associated with cysts, calculi, fibrosis, or necrosis, the outlook for a satisfactory and healthy life is poor.

Actually one of the major problems of the physician caring for such a patient is to maintain morale and to assist in preventing the patient

from becoming a chronic annoyance to his family and associates and an habitual inebriate or drug addict.

Effective treatment can be undertaken only when the status of pancreatic dysfunction is known and the proper type of substitution therapy, diet, and care of associated diseases arranged. This is possible only when the amount of physiologic impairment is understood and followed, since it changes with the progress of the disease.

Summary

Insufficient attention has been given to persistent recurrent pancreatic dyspepsia. Clinicians should be watchful for primary pancreatic dysfunction and become "pancreas conscious" when treating patients with associated diseases. To this end a discussion of the subject has been presented and the aspects of such disturbance in the clinical group entity of chronic relapsing pancreatitis emphasized. Diagnostic criteria and the clinical course have been described. Etiology and pathology have been discussed and the differentiation between primary and secondary relapsing pancreatitis suggested. Nineteen cases of primary disease have been summarized. Details of treatment have been mentioned.

We hope that this report will help to stimulate greater interest in this subject so that earlier diagnosis and more effective treatment can be developed in the future.

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