Chronic Pancreatitis: Diagnosis, Classification, and New Genetic Developments

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The utilization of recent advances in molecular and genomic technologies and progress in pancreatic imaging techniques provided remarkable insight into genetic, environmental, immunologic, and pathobiological factors leading to chronic pancreatitis. Translation of these advances into clinical practice demands a reassessment of current approaches to diagnosis, classification, and staging. We conclude that an adequate pancreatic biopsy must be the gold standard against which all diagnostic approaches are judged. Although computed tomography remains the initial test of choice for the diagnosis of chronic pancreatitis, the roles of endoscopic retrograde pancreatography, endoscopic ultrasonography, and magnetic resonance imaging are considered. Once chronic pancreatitis is diagnosed, proper classification becomes important. Major predisposing risk factors to chronic pancreatitis may be categorized as either (1) toxic-metabolic, (2) idiopathic, (3) genetic, (4) autoimmune, (5) recurrent and severe acute pancreatitis, or (6) obstructive (TIGAR-O system). After classification, staging of pancreatic function, injury, and fibrosis becomes the next major concern. Further research is needed to determine the clinical and natural history of chronic pancreatitis developing in the context of various risk factors. New methods are needed for early diagnosis of chronic pancreatitis, and new therapies are needed to determine whether interventions will delay or prevent the progression of the irreversible damage characterizing end-stage chronic pancreatitis.

Chronic pancreatitis remains a major source of morbidity in the United States. Most patients currently diagnosed with chronic pancreatitis have pain, maldigestion, and, with advancing disease, diabetes mellitus.[1,2] However, intractable pain usually dominates the clinical arena,[2] being recalcitrant to most medical and endoscopic therapies and often recurring after surgical approaches.[3] Hospital admissions average 10 days for these exacerbations,[4] and the need for narcotics is frequent.[4] Patients with long-standing chronic pancreatitis are also at a markedly increased risk of developing pancreatic cancer.[5–10] Because the diagnosis of chronic pancreatitis is usually made after the disease is well established, and because the consequences of chronic pancreatic inflammation and fibrosis appear to be irreversible,[2,11] the prognosis for improvement in those diagnosed with chronic pancreatitis today is dismal.

The phrase "chronic pancreatitis," as commonly used in the clinical context, refers to a syndrome of destructive, inflammatory conditions that encompasses the many sequelae of long-standing pancreatic injury. Histologic changes from the normal pancreatic architecture include irregular fibrosis, acinar cell loss, islet cell loss, and inflammatory cell infiltrates[12–14] (Figure 1). Clinical diagnosis currently depends on identifying defined clinical, functional, morphologic, and histologic features that characterize the final common pathologic pathway of a variety of pancreatic disorders.[15–18] Indeed, the current classification systems of chronic pancreatitis focus on generalized effects of the destructive process rather than etiology,[18] making them more inclusive than precise. The present situation descended from the historical limitations in knowledge of etiology, a disproportionate inclusion of patients with severe (e.g., end-stage alcoholic) chronic pancreatitis, the complexity of obtaining accurate functional and morphologic data from the pancreas of living patients, and an inability to make an early diagnosis and to follow disease progression. The lack of precise classification and stratification systems continues to hinder comparison of clinical studies and frustrates attempts to design new trials to assessing diagnostic or therapeutic interventions. Thus, as recently as 1995, expert state-of-the-science reviewers conceded that "chronic pancreatitis remains an enigmatic process of
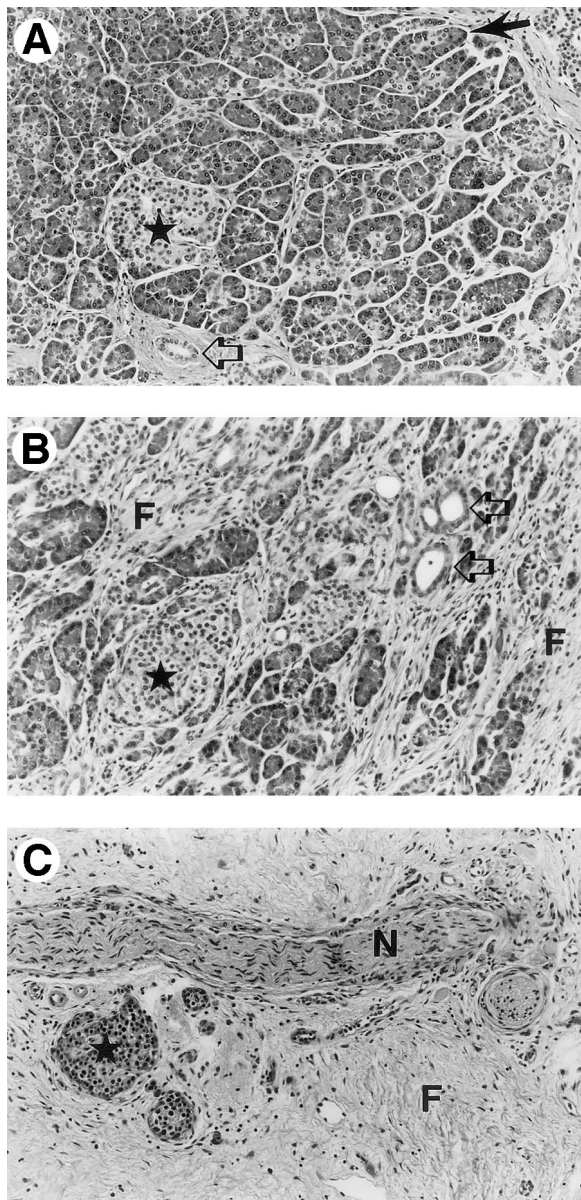
Figure 1. Histology of chronic pancreatitis. (*A*) Minimal chronic pancreatitis; (*B*) moderate chronic pancreatitis; (*C*) advanced chronic pancreatitis. Normal acini (*solid arrow, A*) are lost and replaced by progressive fibrosis (F) associated with fibroblast and lymphocytic infiltration (*B* and *C*). The islets (★) and intralobular pancreatic ducts (*open arrows*) are relatively spared. Note the large nerve branch (N) and complete loss of acinar cell mass typically seen with advanced chronic pancreatitis (*C*).

uncertain pathogenesis, unpredictable clinical course, and unclear treatment."[17]

This review captures a dynamic point in time within the rapid evolution of more broadly accepted definitions, earlier recognition, and efforts to develop more useful classification systems for chronic pancreatic diseases. This sudden movement in the field reflects advances in endoscopic and molecular techniques, identification of new genetic and environmental factors, and a deeper under-

standing of the pathobiology of disease. Improved imaging technologies, including endoscopic ultrasonography (EUS), endoscopic retrograde pancreatography (ERP), and magnetic resonance imaging (MRI), are providing opportunities to detect early morphologic changes in ducts and parenchyma at resolutions of 1 mm or less. The identification of genetic defects associated with chronic pancreatitis, including mutations in the cationic trypsinogen gene (UniGene symbol; PRSS1),[19,20] the pancreatic secretory trypsin inhibitor (UniGene symbol; SPINK1),[21,22] the cystic fibrosis transmembrane conductance regulator (CFTR),[23,24] and preliminary evidence for other disease genes, has provided new opportunities for identifying patients at risk of developing chronic pancreatitis, with the hope of intervention at a much earlier stage.[25,26] These developments demand new paradigms to explain the pathophysiologic processes. Although new information continues to be discovered, defined, and assimilated, a review of recent progress and state-of-the-art diagnostic techniques for chronic pancreatitis will be useful for the informed clinician.

This review will focus on the definitions and classification of chronic pancreatitis, on structural and genetic analysis, and on risk factors. For secondary treatment options, the reader is referred to other excellent reviews on this topic.[3,27–29]

Classification and Definitions

Chronic pancreatitis has been defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of function.[18,30,31] This definition proves useful for generally separating chronic pancreatitis from acute pancreatitis. However, distinguishing the effects of acute pancreatitis from chronic pancreatitis solely on clinical grounds over a limited time remains difficult.[15] Classification of the various forms of chronic pancreatitis within this definition is likewise challenging.

An ideal disease classification system for chronic pancreatitis would be simple, objective, accurate, and relatively noninvasive, incorporating etiology, pathogenesis, structure, function, and clinical status into one overall schema.[32,33] Although these criteria have never been met, several systems have been advanced. The most widely used classification systems include the Marseille classification of 1963[30,34] with revisions in 1984[35] and 1988,[36] and the Cambridge classification of 1984[37,38] (Table 1). The Marseille system distinguishes acute from chronic pancreatitis rather clearly: acute pancreatitis must lead to clinical, histologic, and functional resolution of disease

Table 1. Marseille and Cambridge Classification Systems

	Definitions			
Term	Marseille 1963	Marseille 1984	Marseille–Rome 1988	Cambridge
Acute pancreatitis				
Morphologic	Gradation of lesions from interstitial edema to peripancreatic fat necrosis, parenchymal necrosis, and hemorrhage. Morphologic restitution is rule if primary cause or factor eliminated	No major changes	No major changes	No specifics defined. Restitution to normal is rule if primary cause or factor eliminated
Functional	No discussion or exploration of relationship between anatomic and functional changes	Exocrine and endocrine function impaired to variable extent and variable duration. No other specifics included. Resolution to normal is rule if primary cause or factor eliminated	No major changes	No specifics defined
Clinical	No specific comments	Acute abdominal pain with increased pancreatic enzymes in blood or urine. Usual benign course, although severe attacks may be fatal. May be single attack or recur	No major changes	Acute condition typically presenting with abdominal pain, and usually associated with raised pancreatic enzymes in blood or urine, due to inflammatory disease of the pancreas
Acute relapsing pancreatitis				
Morphologic	Same as acute pancreatitis	Eliminated	—	—
Functional	Same as acute pancreatitis	Eliminated	—	—
Clinical	No specific comments except for temporally "frequent" attacks	Eliminated	—	—
Chronic pancreatitis				
Morphologic	Irregular sclerosis with destruction and loss of exocrine parenchyma, either focal, segmental, or diffuse. Dilation of ductal system associated with strictures or stones. Inflammatory cells may be present. Islets relatively spared in comparison to acini; all histologic features may be seen in all etiologies. Irreversible damage present	Essentially same but with subclassifying descriptors including "chronic pancreatitis with focal necrosis," "chronic pancreatitis with segmental or diffuse fibrosis," and "chronic pancreatitis with or without calculi" "Obstructive chronic pancreatitis" listed as distinct form, characterized by dilation of ductal system proximal to occlusion of major duct, diffuse atrophy of acinar parenchyma, and uniform diffuse fibrosis with calculi uncommon	Addition of "chronic calcifying pancreatitis" and "chronic inflammatory pancreatitis" as distinct forms	Continuing inflammatory disease with irreversible morphologic change
Functional	No discussion or exploration of relationship between anatomic and functional changes	With exception of obstructive form, progressive or permanent loss of exocrine and endocrine function is rule. In obstructive form, functional changes improve when obstruction is removed	No further elaboration	Permanent loss of function; no further comments
Clinical	No specific comments	Characterized by recurrent or persistent abdominal pain, though may present without pain. Evidence of insufficiency (steatorrhea, diabetes) may be present	No further elaboration	Pain often present but not required. Pancreatic pain in absence of detectable morphologic abnormality acknowledged but not formally classified Classification of severity based on US, CT, and ERCP adopted
Chronic relapsing pancreatitis				
Morphologic	Same as chronic pancreatitis	Eliminated	—	—
Functional	No specific comments	Eliminated	—	—
Clinical	Attacks of clinical pancreatitis (not specifically defined) in background of morphologically abnormal gland	Eliminated	—	—

once the instigating factor has been removed. Chronic pancreatitis, on the other hand, requires permanent histologic irregularity, often (but not always) associated with persistent clinical and functional impairment. This system relies heavily on the presence of characteristic pain. The two revisions in the original classification attempted to better categorize histopathologic findings to intimate common etiologic pathways leading to disease. The most recent Marseille–Rome classification of 1988[36] includes more causal factors. However, this sys-

tem proves more useful in defining chronic pancreatitis than serving as a classification system. The Cambridge classification uses imaging tests to provide a grading and severity system.[37,38] It also differentiates acute and chronic pancreatitis, noting that a single episode of acute pancreatitis may have implications on pancreatic morphology and function.[39] However, these classifications do not distinguish the different forms of chronic pancreatitis on the basis of etiology, nor do they help to clinically distinguish patients or the functional abnormalities associated with those specific etiologies. Thus, the Cambridge system proves more useful as a staging system once the diagnosis is made rather than a system for classifying the etiologies of chronic pancreatitis. Other systems have also been proposed (e.g., a clinically based classification system for alcoholic chronic pancreatitis[40] and a clinical-etiology system for chronic calcifying pancreatitis[41]), but are not widely accepted. The limitations of current classification, staging, and reporting systems become clear when attempting to compare studies,[42] and they are especially apparent when trying to classify patients with exocrine pancreatic insufficiency and normal duct systems, and vice versa.[39] These observations emphasize the reality that different disorders causing similar-appearing injury to the pancreas may follow different clinical courses. Thus, clear definitions of chronic pancreatitis, an etiology-based classification system, and functional, structural, and morphologic staging systems are needed.[41] Indeed, efforts are underway to develop such a system and test it prospectively (M.W. Büchler, personal communication, August 2000).

Incidence, Prevalence, and the Spectrum of Disease

The reported incidence, prevalence, and manifestations of chronic pancreatitis with overt disease underestimate the true spectrum of this disorder. Earlier series from Copenhagen,[43] the United States,[44] and Mexico City[45] reported similar incidence of about 4 per 100,000 inhabitants per year and prevalence rates of about 13 per 100,000 inhabitants. Subsequent changes in alcohol consumption throughout the world[46–48] and the improved sensitivity of diagnostic tests lead many to believe that there are far more patients with chronic pancreatitis than initially suspected. For example, in a recent study from Japan, 68% of patients with chronic pancreatitis were diagnosed with the use of computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), or other advanced techniques leading to an estimated overall prevalence rate of 45.4 per 100,000 in males and 12.4 per 100,000 in females.[49] Recognition of high-risk

groups with less striking clinical features than alcoholics (e.g., genetically predisposed individuals, patients with end-stage renal disease) may also effect these estimates. Readdressing the epidemiology of chronic pancreatitis using new criteria and better techniques will be important for determining public health care policy and appropriating resources for clinical care and research.

Diagnosis of Chronic Pancreatitis

The following sections present the process of diagnosing, classifying, and staging chronic pancreatitis. The reader should recognize that limited consensus exists on these issues, especially on the interpretation and classification of abnormal function test results in the presence of normal imaging study results. The algorithms presented (Figure 2) represent the opinion of the authors and have been reviewed and approved by a majority of the members of the Midwest Multicenter Pancreatic Study Group (MMPSG). A minority view is that, because of the practical unavailability of pancreatic biopsy, an abnormal function test is nearly diagnostic of chronic pancreatitis. Other approaches have been advanced and represent, in part, the expertise of the local institutions.

The diagnosis of chronic pancreatitis can be made by histologic or morphologic criteria alone, or by a combination of morphologic, functional, and clinical findings.[14,18,39,41,50] Functional abnormalities alone are not diagnostic of chronic pancreatitis because these tests do not differentiate chronic pancreatitis from pancreatic insufficiency without pancreatitis. Despite this fact, some experts include abnormal function testing results in diagnostic criteria, e.g., the diagnostic criteria adopted by the Japan Pancreas Society[14] (Table 2). This practice may be based on the observation that other acquired causes of pancreatic insufficiency are uncommon. However, we believe diagnosis of chronic pancreatitis based on function testing alone leads to confusion and controversy and ignores the histologic definition of chronic pancreatitis. Clearly, the diagnosis of severe chronic pancreatitis with extensive calcifications and ductal dilation is simple. The difficulty in diagnosis arises in patients with early, mild, or minimal change pancreatitis,[51] characteristic pancreatic pain alone, patients in whom chronic pancreatitis is being differentiated from a pancreatic malignancy, and in patients with a recent episode of acute pancreatitis.[18]

Selection of the appropriate diagnostic test depends on what the clinician is attempting to diagnose. Fecal fat measurements, for example, detect fat in the stool. If the patient is on a proper diagnostic test diet, then excess fecal fat usually reflects maldigestion or malabsorption, which may be caused by chronic pancreatitis, pancreatic
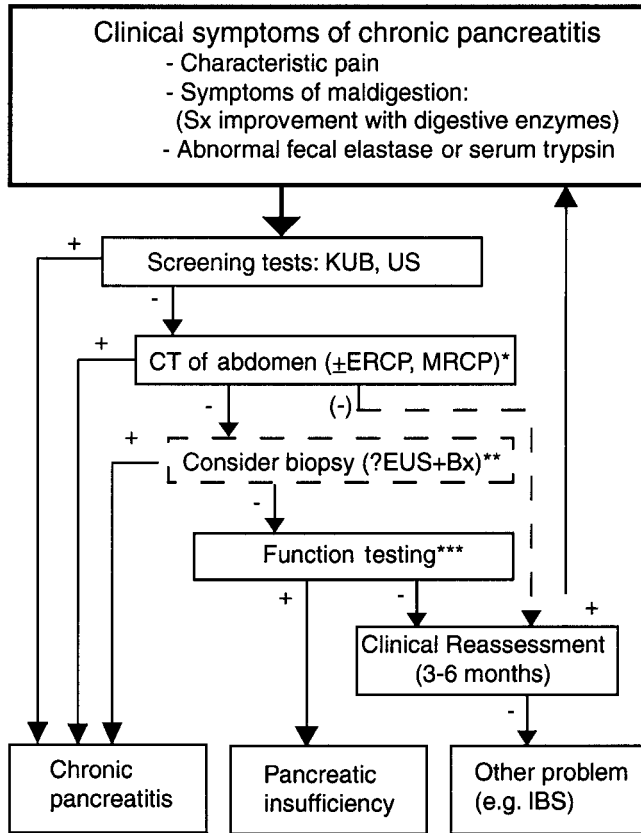
Diagnosis of Suspected Chronic Pancreatitis

Figure 2. Algorithm for the evaluation of suspected chronic pancreatitis. If clinical and laboratory symptoms suggest chronic pancreatitis, the diagnostic algorithm is entered. Many experts begin the evaluation with a transabdominal ultrasound (US) examination or abdominal x-ray (KUB), whereas others proceed directly to CT scan. *CT is preferred to ERP and MRI at this stage, although similar information is obtained. If the CT is nondiagnostic of chronic pancreatitis, either biopsy (*solid arrow*) or reassessment (*dashed line*) should be considered. In centers where EUS is not available, ERP is often used after nondiagnostic CT, especially if recurrent pancreatitis is also being considered. **Biopsy is the gold standard but is usually not available, and the risk of pancreatitis remains a major concern. The ability to combine EUS with biopsy remains experimental presently. The role of EUS without biopsy in diagnosing chronic pancreatitis is promising but controversial (see Endoscopic Ultrasonography in text). Thus, this step remains within a *dashed box*, implying its likely future position. ***Pancreatic function testing in the presence of normal imaging test result and/or biopsy represents pancreatic insufficiency until proven otherwise. If the CT or other imaging techniques are indeterminate, then function testing may be used as supporting evidence of chronic pancreatitis, but not proof. If one test in the algorithm is not available, the next listed test should be used. Sx, symptoms; Bx, biopsy; IBS, irritable bowel syndrome.

insufficiency (primary or secondary), intestinal pathology, or other problems (Table 3). Thus, understanding the purpose, uses, and limitations of a variety of diagnostic tests is essential when evaluating pancreatic disease. Because the focus of this review is on the diagnostic testing for chronic pancreatitis rather than pancreatic

insufficiency, our emphasis will be on tissue evaluation, imaging studies, and genetic analysis.

The Gold Standard

The ideal diagnostic test for chronic pancreatitis should be sensitive, specific, accurate and reliable, widely available, inexpensive, easy to perform, and at no or low risk to the patient. The evaluation of diagnostic methods in current clinical practice must be mindful that a gold standard and definition of chronic pancreatitis remains in question.[18] However, as in other diseases, tissue diagnosis must be the gold standard. Any persistently abnormal inflammatory state or distortion of the normal architecture may serve as strong evidence for chronic pancreatitis, because the correlation with the tissue biopsy "gold standard" is high in the later stages of the disease.[52]

Table 2. Diagnostic Criteria for Chronic Pancreatitis: Japan Pancreas Society

Definite chronic pancreatitis
  1. (a) Ultrasonography: pancreatic stones evidenced by intrapancreatic hyperreflective echoes with acoustic shadows behind
     (b) CT: pancreatic stones evidenced by intrapancreatic calcifications
  2. ERCP: (a) irregular dilatation of pancreatic duct branches of variable intensity with scattered distribution throughout the entire pancreas or (b) irregular dilatation of the main pancreatic duct and branches proximal to complete or incomplete obstruction of the main pancreatic duct (with pancreatic stones or protein plugs)
  3. Secretin test: abnormally low bicarbonate concentration combined with either decreased enzyme outputs or decreased secretory volume
  4. Histologic examination: irregular fibrosis with destruction and loss of exocrine parenchyma in tissue specimens obtained by biopsy, surgery, or autopsy; fibrosis with an irregular and patchy distribution in the interlobular spaces; intralobular fibrosis alone not specific for chronic pancreatitis
  5. Additionally, protein plugs, pancreatic stones, dilation of the pancreatic ducts, hyperplasia and metaplasia of the ductal epithelium, and cyst formation
Probable chronic pancreatitis
  1. (a) Ultrasonography: intrapancreatic coarse hyperreflectivities, irregular dilatation of pancreatic ducts, or pancreatic deformity with irregular contour
     (b) CT: pancreatic deformity with irregular contour
  2. ERCP: irregular dilatation of the main pancreatic duct alone; intraductal filling defects suggestive of noncalcified pancreatic stones or protein plugs
  3. (a) Secretin test: (i) abnormally low bicarbonate concentration alone or (ii) decreased enzymes outputs plus decreased secretory volume
     (b) Tubeless tests: simultaneous abnormalities in BT-*p*-amino benzoic acid and fecal chymotrypsin tests observed at 2 points several months apart
  4. Histologic examination: intralobular fibrosis with one of the following findings: loss of exocrine parenchyma, isolated islets of Langerhans, or pseudocysts

Data from Homma et al.[14]

Table 3. Causes of Pancreatic Insufficiency Without Pancreatitis

Primary pancreatic insufficiency
  Agenesis of the pancreas
  Congenital pancreatic hypoplasia
  Shwachman–Diamond syndrome
  Johanson–Blizzard syndrome
  Adult pancreatitic lipomatosis or atrophy
  Isolated lipase deficiency
  Pancreatic resection
Secondary
  Mucosal small bowel disease: decreased cholecystokinin release
  Gastrinoma: intraluminal destruction of enzymes
  Billroth II anastomosis: poor mixing or decreased hormone release
  Enterokinase deficiency
  Kwashiorkor: protein calorie malnutrition

Diagnostic pancreatic tissue biopsies are seldom available so that a "gold standard" diagnosis must often be deferred (Figure 2). However, the gold standard must remain a tissue diagnosis.

Pancreatic Tissue Sampling

Because the diagnosis of chronic pancreatitis pivots on pathologic changes in the pancreas, obtaining tissue for evaluation is a primary consideration. Surgical sampling of the pancreas through laparoscopy or laparotomy can safely provide significant amounts of tissue for confirming the diagnosis of chronic pancreatitis. But the labor, expense, and surgery-related risk of this approach must be weighed against other methods of obtaining tissue. In particular, if there is the need to periodically assess the presence or progress of disease, repeated surgical procedures are impractical and other methods of obtaining tissue must be considered.

Percutaneous core needle biopsy, guided by either ultrasonography or CT, has been successfully performed for more than 2 decades.[53] It is an accurate and reliable way of sampling the pancreas and is relatively safe, with a reported complication rate of 0.8%–1.1%,[54,55] although anecdotal experience suggests that the rate may be higher in a nearly normal pancreas. Despite its relative safety, percutaneous biopsy of the pancreas is not often used in the United States for diagnosing chronic pancreatitis. Indeed, anecdotal experience would suggest that an ERP would more likely be used to confirm the diagnosis despite its own risks.[56] This alone does not suggest that percutaneous biopsy is the most appropriate method of obtaining gold standard diagnostic information. Indeed, some etiologies of chronic pancreatitis, including alcohol, hereditary, autoimmune, and "idiopathic" pancreatitis, display patchy abnormalities in pancreatic parenchyma,[13,14,57] raising the possibility that a single random biopsy may not be diagnostic. Thus, a more sensitive and targeted technique than CT scan or routine transabdominal ultrasound examination is being considered for directed biopsies. EUS-guided biopsies may have similar or better levels of safety as percutaneous biopsy, thereby providing another method of obtaining pancreatic tissue for diagnosing chronic pancreatitis. This technique has not been perfected and is not widely available. However, regardless of the method used, we believe that tissue confirmation of suspected chronic pancreatitis must be considered the gold standard, just as biopsy serves as the gold standard for most other diseases. Therefore, tissue biopsy is included as a key step in the diagnostic algorithm for chronic pancreatitis in anticipation of the necessary advances in technology and experience (Figure 2).

Structural Imaging of the Pancreas to Diagnose Chronic Pancreatitis

Four imaging procedures are commonly used for the evaluation of pancreatic disease: CT, ERP, EUS, and MRI. Chronic pancreatitis with calcifications can also be identified on abdominal x-rays or by transabdominal ultrasound examination, and when present, the diagnosis of chronic pancreatitis can be made with 90% confidence.[16] These techniques are used as inexpensive initial screening techniques in some centers.[16] However, these imaging techniques lack the sensitivity of CT, ERP, and EUS.[18] Extensive experience and availability exists with CT and ERP, and both of these techniques seem to be reaching their theoretic technical limits. EUS and MRI continue to be developed and tested, are less widely available, require more technical expertise, and their eventual role in evaluation of chronic pancreatitis remains to be fully defined. Each of these newer technologies offers significant advantages and promise over ERP or CT, but they also have limitations.

Computed Tomography

The abdominal CT scan should be the first test in the evaluation of possible chronic pancreatitis because it is noninvasive, widely available, and has relatively good sensitivity for diagnosing moderate-to-severe chronic pancreatitis.[52,58–60] It is useful in identifying most complications of chronic pancreatitis, and it reproducibly visualizes inflammatory or neoplastic masses larger than 1 cm.[18,61] Pancreatitis is diagnosed by CT with the identification of pathognomonic calcifications within the pancreatic ducts or parenchyma, and/or dilated main pancreatic ducts combined with parenchymal atrophy
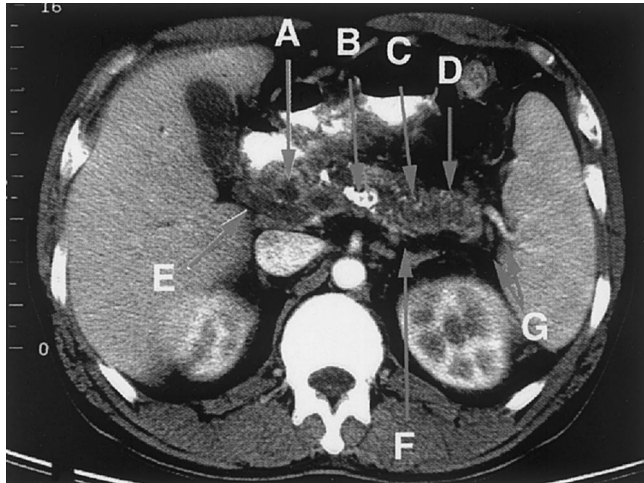
Figure 3. Contrast-enhanced CT image of the abdomen showing severe chronic pancreatitis. Major complications of chronic pancreatitis include (A) pseudocysts, (B) calcifications, (C) dilated ducts, (D) pancreatic parenchymal atrophy, (E) dilated common bile duct, (F) splenic vein thrombosis, and (G) gastric varices. (Reprinted with permission from www.pancreas.org.)

(Figure 3). An abdominal CT is also useful in the evaluation of pain when chronic pancreatitis is high on the differential diagnosis because CT may also help identify peripancreatic and other abdominal abnormalities that may mimic chronic pancreatitis clinically such as pancreatic cancer.

Optimal evaluation of the pancreas requires helical CT scanning using a pancreas-optimized protocol.[60,62,63] Water should be used as an oral contrast agent to maximize pancreatic visualization, and especially the duodenal wall, the papilla, and the duodenal pancreatic interface.[61] An initial scan without intravenous contrast will easily identify pancreatic calcifications (Figure 4). This should be followed by contrast infusion using a pancreatic cancer protocol[61,64] to allow for optimal enhancement of early tumors. About 150 mL of contrast are rapidly infused (3–5 mL/s) with 3.5–5-mm sections taken after a 35–40-second delay (pancreatic phase). The scan is repeated after 60–70 seconds with 5–7-mm-thick sections to identify venous obstruction/invasion by tumor, the biliary tree, and the liver parenchyma with possible pancreatic cancer metastases (liver/portal venous phase). Examinations can be completed in a few minutes and characteristic features of chronic pancreatitis identified, including cysts, calcifications, and a dilated or tortuous main pancreatic duct.

The current sensitivity and specificity of CT are unknown. In patients with early chronic pancreatitis, the role of CT may be limited. Some studies suggest CT may detect fine parenchyma changes in early chronic pancreatitis[60] and may identify features suggestive of autoim-

mune chronic pancreatitis.[65] However, because of the technical limitations of CT, the earliest changes of chronic pancreatitis may not be identified. Thus, CT remains the best screening tool for detection of chronic pancreatitis and exclusion of other intraabdominal disorders that may cause symptoms indistinguishable from chronic pancreatitis on clinical grounds alone. A tissue biopsy may be necessary when no morphologic changes are visible on CT and the diagnosis is important in the clinical decision making process.

Endoscopic Retrograde Pancreatography

In the absence of tissue confirmation, ERP must be considered as a sensitive and specific test for the diagnosis of chronic pancreatitis, with sensitivity and specificity in earlier reports approaching 90% and 100%, respectively.[66] However, these estimates depend on the disease and control populations studied and on the choice of a gold standard. Enrichment of the study populations with older patients who may develop benign pancreatic duct changes without pancreatitis,[67] patients with recent acute pancreatitis with duct changes, or patients with chronic epigastric pain vs. a histologic gold standard would likely decrease these sensitivity and specificity estimates for ERP.

In mild or early disease, findings include dilation and irregularity of the smaller ducts and branches of the pancreas (Figure 5). In more moderate disease, these changes are found in the main pancreatic duct as well. Tortuosity, stricture, calcifications, and cysts may also be seen as disease becomes more severe. Although the ductography seen in severe disease is pathognomonic, the more subtle changes seen in minimal disease are subject to variability in interpretation and difficulty in distinguishing normal from abnormal. The Cambridge classi-
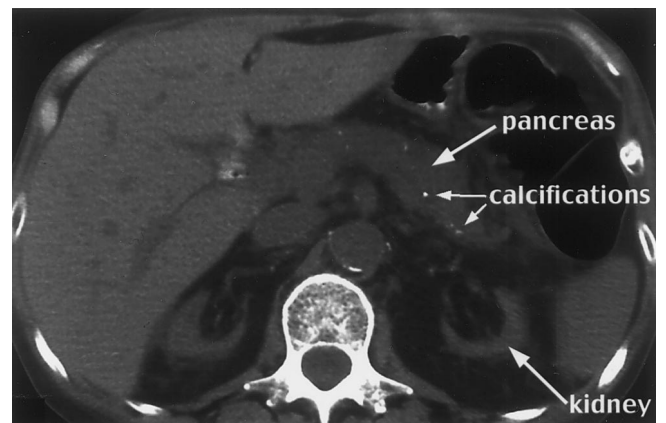

Figure 4. Noncontrast CT image of the abdomen showing chronic pancreatitis in the context of chronic renal insufficiency. Note pancreatic calcifications and atrophic kidneys.

Figure 5. ERP in chronic pancreatitis. (*A*) Normal pancreatic duct. (*B*) Mildly dilated duct with side branch dilatation and small intrapancreatic duct stones. (*C*) Severe chronic pancreatitis with markedly dilated main pancreatic duct, numerous dilated side branches, and multiple intraductal pancreatic stones. The diameters of the ducts are 2, 4, and 8 mm, respectively. (Reprinted with permission from www.pancreas.org.)
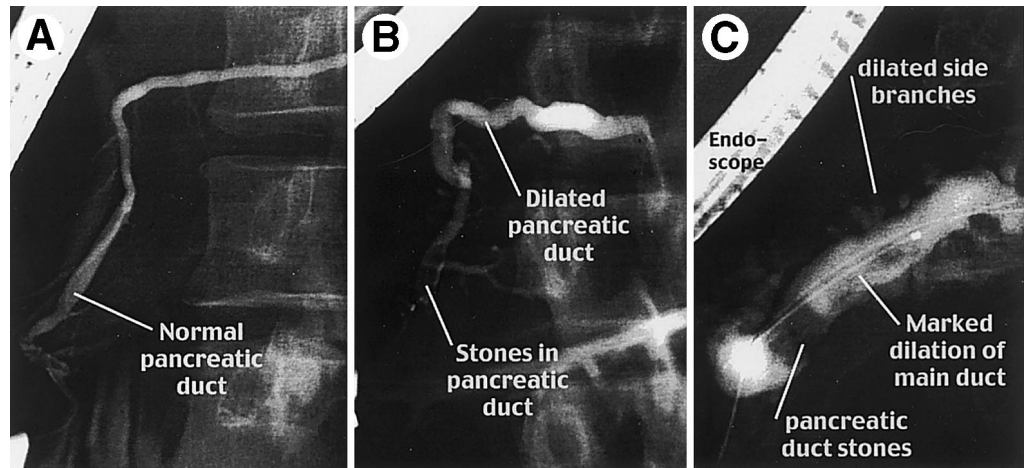
fication (Table 1) is the most commonly used method of classifying severity of disease, with other classification schemes sometimes used as well.[68] These schema, however, suffer from difficulties in interpretive differences because of variability in technique and, in addition to the recognition of patients with signs and symptoms of chronic pancreatitis with minimal to no changes on ductography (minimal change pancreatitis), suggest that current ERP methods may not be capable of detecting a potentially large group of patients with early disease. The small but significant risk and the expense of ERP also places ERP in a secondary role in the diagnosis of chronic pancreatitis. ERP remains useful for those patients in which other methods are nondiagnostic or unavailable, in patients with a clinical pattern of recurrent acute pancreatitis, or when a therapeutic intervention is being considered.[69] The role of ERP in the evaluation of those patients suspected of having sphincter of Oddi dysfunction as a contributor to acute recurrent pancreatitis or chronic pancreatitis continues to be evaluated.

Endoscopic Ultrasonography

EUS is likely to play an increasingly important role in the evaluation and management of patients with chronic pancreatitis. By placing a high frequency (5 Mz to 30 MHz) probe in close approximation to the pancreas, high resolution (<1 mm) images of pancreatic parenchyma and duct structure can be generated without the use of ionizing radiation. Several endosonographic features have been noted in patients with chronic pancreatitis[70] (Figure 6). Two series totaling 27 patients have reported histologic correlation to these features, but detailed correlation between a histologic feature and its expected EUS correlate (i.e., hyperechoic strands to parenchymal fibrosis) is lacking. EUS may also be used to obtain tissue and/or pancreatic juice during the examination. This ability to combine imaging with measures of pancreatic function, histology, and molecular markers may make EUS the test of choice for diagnosing and following patients with chronic pancreatitis (Figure 2). Important issues, however, need to be addressed. First, "normal" features need to be more clearly defined. The normal endosonographic appearance of the pancreas has been described in young, healthy medical students.[71] The known pathologic changes in the pancreas associated with aging[67] need correlation to EUS imaging, as should the changes associated with obesity or lower lean body mass. Second, interobserver variability in interpretation must be carefully evaluated. Although recent data suggest a correlation between experienced individuals in some features,[72] further work to standardize interpretation is needed. Differences in transducer and processor technology as well as the specific settings on both the processor and monitor will also need to be considered. Finally, other issues including image enhancement via different frequencies, postimage computer processing,[73] and molecular imaging markers[74] need further attention. Finally, efforts to standardize EUS training are under way.[75]

Despite these limitations in standardization and correlation, the anticipated technical advances and diagnostic capabilities of combining high-resolution images with directed pancreatic biopsies should solidify this modality as the diagnostic tool of choice in cases in which chronic pancreatitis is suspected and early diagnosis is important.

Magnetic Resonance Imaging

The use of MRI to perform magnetic resonance cholangiopancreatography (MRCP) is evolving as an important tool in the evaluation of chronic pancreatitis (Figure 7). MRCP is noninvasive, avoids ionizing radiation and contrast administration, and does not routinely require sedation, making it a diagnostic procedure of
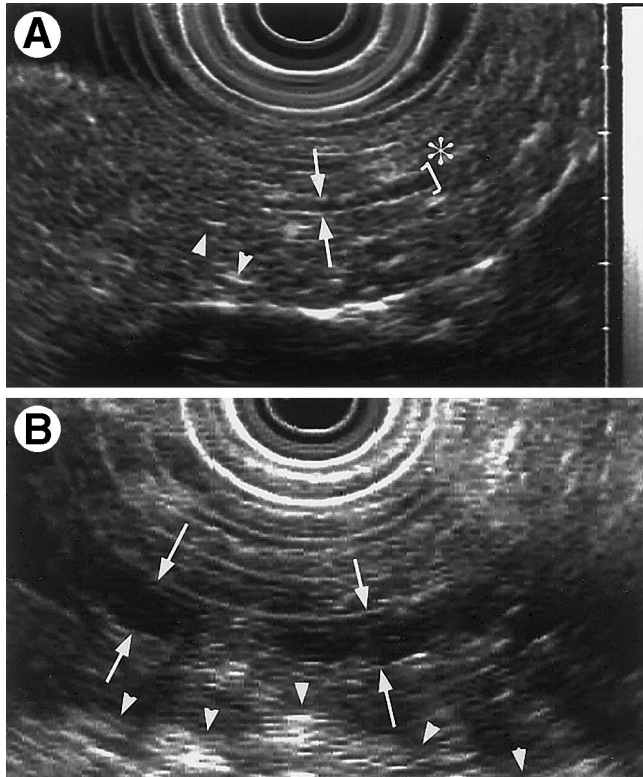
Figure 6. EUS showing mild and severe chronic pancreatitis. (*A*) Changes associated with mild chronic pancreatitis include mild irregularity and dilation of the main pancreatic duct (*), hyperechoic duct margins (*arrows*), and hyperechoic stranding in the pancreatic parenchyma (*arrowheads*). (*B*) Severe chronic pancreatitis with lobular outline of the pancreas (*arrowheads*), dilation of the main pancreatic duct (*arrows*), and hyperechoic stranding in milder disease.

choice in some groups of patients, particularly children. When combined with conventional abdominal MRI, MRCP can provide comprehensive information on the pancreas and peripancreatic tissues.[76] Like EUS, it potentially has a resolution that approaches 1 mm. In addition, some work has been done in evaluating potential functional information after intravenous secretin injection and the measurement of pancreatic and duodenal fluid volume changes in response to the stimulus.[77,78] However, because of wide range of values in fluid output between patients with a normal pancreas and chronic pancreatitis, MRCP cannot be used as a reliable noninvasive function test, unless bicarbonate concentration can be measured.

Our institution uses a 1.5-T field strength superconducting magnet (Signa; GE Medical Systems, Milwaukee, WI) with torso phased array coil to improve image quality. After a coronal localizer sequence is obtained to prescribe locations for axial images, T2-weighted fat suppressed fast spin echo sequences are acquired of the abdomen. MRCP images are then obtained with single

shot, fast spin echo sequences during 2-second suspended respirations.

Although studies have begun to demonstrate the important role MRI and MRCP can play in the diagnosis and staging of pancreatic cancer,[79] investigation into their role in chronic pancreatitis has only recently begun.[80,81] Major lesions such as grossly dilated ducts, communicating pseudocysts, and even pancreas divisum can be detected. But small duct changes and calcifications are not readily detected, and the modality does not have therapeutic potential.

Functional Testing in the Evaluation of Chronic Pancreatitis

The pancreas has significant functional reserve, so that it must be damaged significantly before functional loss is clinically recognized.[82] Invasive tests of pancreatic function (e.g., the "tubed" secretin test) are the gold standard for determining exocrine pancreatic function. Indeed, chronic pancreatitis and diminished pancreatic function go hand in hand,[11,83] but the latter is not diagnostic of the former. Thus, pancreatic function testing is not diagnostic of chronic pancreatitis, but rather serves as a sign of chronic pancreatitis and a measure of the severity of injury. Excellent reviews of pancreatic function testing are available,[16,18,84–87] and the intricacies of each will not be addressed here.

Pancreatic function testing serves three purposes: to diagnose pancreatic insufficiency, to aid in the evaluation of chronic pancreatitis, and to provide a basis for rational treatment.[86] Mechanistically, pancreatic insufficiency reflects either impaired enzyme synthesis capacity, altered
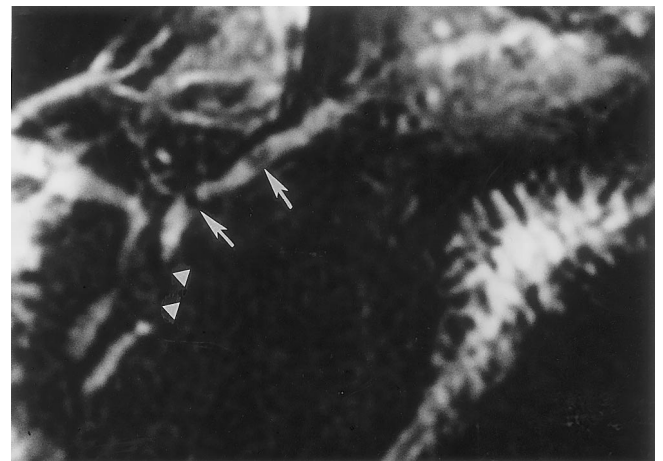

Figure 7. MRCP showing chronic pancreatitis. MRCP image of the pancreas in a patient with moderate chronic pancreatitis. The pancreatic duct appears dilated and contains short strictures (*arrows*) and a large stone (*arrowhead*). The image closely parallels findings on a subsequent ERP (not shown).

release of enzymes and bicarbonate into the intestine, or intraluminal impairment of pancreatic enzyme function or mixing.[85] Pancreatic function tests are difficult to compare among centers because they often use different stimulants and measure different parameters.[85] Furthermore, the lack of appropriate control populations and technical variability makes the test difficult to interpret. Thus, few centers perform direct testing of pancreatic exocrine secretion. Noninvasive function test to detect pancreatic insufficiency is also used infrequently because it is both insensitive and it has a high false-positive rate.[86]

The limitations of function testing in diagnosing chronic pancreatitis are recognized in several published systems for diagnosing chronic pancreatitis.[14,39,88] In each of these systems, chronic pancreatitis is diagnosed with a single "diagnostic" imaging study (e.g., histology, typical CT scan, ERCP, or ultrasound identifying calcifications). Abnormal function test results alone are not diagnostic of chronic pancreatitis in the scoring systems from the Mayo Clinic[88] or Lüneburg Clinic.[39] Although an abnormal secretin test does meet diagnostic criteria for chronic pancreatitis in the Japan Pancreas Society criteria[14] (Table 2), this criteria has been questioned.[39]

Etiology and Risk Factors: Cause and Classification

Recent advances in genetics and technology provide new possibilities for accurate and early identification of risk factors leading to chronic pancreatitis. The following section outlines the major risk factors associated with the development of chronic pancreatitis categorized according to toxic-metabolic causes, idiopathic, genetic, autoimmune, recurrent severe acute pancreatitis–associated chronic pancreatitis, and obstructive chronic pancreatitis (TIGAR-O risk factor classification system version 1.0; Table 4). The classification is roughly based on prevalence of each etiology, and each class has implications for potential treatment.[41] Special attention is given to genetic testing.

Spectrum of Etiology

With few exceptions, the exact etiology of most cases of chronic pancreatitis is only partially known. For example, excessive alcohol consumption alone does not cause chronic pancreatitis in animals or humans. Thus, other yet-to-be-identified genetic or environmental factors must be present before alcoholic pancreatitis develops. Likewise, several of the genetic mutations associated with chronic pancreatitis, including mutations in CFTR gene or SPINK1 alone, cannot be disease causing, be-

Table 4. Etiologic Risk Factors Associated With Chronic Pancreatitis: TIGAR-O Classification System (Version 1.0)

Toxic-metabolic
  Alcoholic
  Tobacco smoking
  Hypercalcemia
    Hyperparathyroidism
  Hyperlipidemia (rare and controversial)
  Chronic renal failure
  Medications
    Phenacetin abuse (possibly from chronic renal insufficiency)
  Toxins
    Organotin compounds (e.g., DBTC)
Idiopathic
  Early onset
  Late onset
  Tropical
    Tropical calcific pancreatitis
    Fibrocalculous pancreatic diabetes
  Other
Genetic
  Autosomal dominant
    Cationic trypsinogen (Codon 29 and 122 mutations)
  Autosomal recessive/modifier genes
    CFTR mutations
    SPINK1 mutations
    Cationic trypsinogen (codon 16, 22, 23 mutations)
    α_1-Antitrypsin deficiency (possible)
Autoimmune
  Isolated autoimmune chronic pancreatitis
  Syndromic autoimmune chronic pancreatitis
    Sjögren syndrome–associated chronic pancreatitis
    Inflammatory bowel disease–associated chronic pancreatitis
    Primary biliary cirrhosis–associated chronic pancreatitis
Recurrent and severe acute pancreatitis
  Postnecrotic (severe acute pancreatitis)
  Recurrent acute pancreatitis
  Vascular diseases/ischemic
  Postirradiation
Obstructive
  Pancreatic divisum
  Sphincter of Oddi disorders (controversial)
  Duct obstruction (e.g., tumor)
  Preampullary duodenal wall cysts
  Posttraumatic pancreatic duct scars

cause only a small fraction of individuals who inherit these mutations ever develop pancreatitis. Therefore, the TIGAR-O risk factor classification system lists factors reported to be associated with chronic pancreatitis and categorizes patients according to the factor most strongly associated with pancreatitis in a particular patient. For example, a person with the cationic trypsinogen gene mutation R112H (80% likelihood of developing pancreatitis and approximately 40% likelihood of developing chronic pancreatitis) who consumes some alcohol (<10% likelihood of chronic pancreatitis) would be categorized under "genetic" predisposition rather than "toxic-metabolic" predisposition.

Determination of etiology continues to grow in importance as more forms of chronic pancreatitis are identified at earlier stages. Knowledge of etiology remains central to clinicopathologic studies, multifactorial analysis, understanding of the natural and clinical history of each chronic pancreatitis-producing disorder, and development of preventative and therapeutic strategies.[40] Hints as to the importance of these observations are already beginning to emerge.[22,88] Several current paradigm shifts in our understanding of chronic pancreatitis involve the role of the ducts,[89–91] lithostathin,[92–94] trypsinogen activation in the acinar cell,[25,95] stellate cell activation and fibrosis,[96–98] and genetics.[26] Several of the factors clearly associated with the development of chronic pancreatitis are presented.

Toxic and Metabolic Factors Associated With Chronic Pancreatitis

Alcohol. A relationship between alcohol and chronic pancreatitis has been suggested for more than 50 years,[99] and alcoholism is now reported to be the dominant cause of chronic pancreatitis in industrialized nations worldwide. Alcohol use preceded disease in 55%–80% of patients with chronic pancreatitis.[15–17,49,100,101] The onset of alcoholic chronic pancreatitis appears to occur after consuming 144 ± 79 g alcohol per day (mean $\pm$ SD) for 19 years in Marseille, France,[102] 150 ± 89 g/day for 17 years in Europe and South Africa (white subjects),[102] and 397 ± 286 g/day (range, 80–1664 g/day) for 21 years (range, 4–44 years) in Brazil.[101] These data suggest that heavy alcohol consumption causes pancreatitis in humans.

However, this type of observational data does not prove that alcohol consumption causes chronic pancreatitis independent of more important and dominant genetic or environmental factors whose identity currently elude us. For example, why do only about 10% of heavy alcohol drinkers ever suffer from clinically recognized pancreatic disease?[103,104] Furthermore, in the preliminary report of Kalthoff et al. from the Mayo Clinic,[105] more than 30% of patients in whom alcohol was considered to be the contributing cause of chronic pancreatitis had "social" or "uncertain" levels of alcohol intake,[16] suggesting either marked heterogeneity in susceptibility or misclassification of some patients. Although the risk of chronic pancreatitis increases as a function of the quantity of alcohol consumption, there is no apparent threshold of toxicity.[102] Indeed, the relationship between alcohol consumption and chronic pancreatitis is weak compared with the association between alcohol consumption and liver cirrhosis and other common alcohol-related problems.[106] Laboratory studies also raise major ques-

tions because long-term, high-dose alcohol feeding of animals fails to cause chronic pancreatitis.[107,108] Thus, in our opinion, alcohol seems to be a cofactor in the development of chronic pancreatitis in susceptible humans.

Additional evidence for a genetic basis for alcoholic pancreatitis comes from epidemiology studies.[109] In comparison with white patients, black patients are 2–3 times more likely to be hospitalized for chronic pancreatitis than alcoholic cirrhosis.[110] However, the underlying genetic factor has remained elusive. Although candidate genes have been studied including aldehyde dehydrogenase polymorphisms,[111,112] HLA antigens,[113–117] CFTR,[23,24] cationic trypsinogen,[118,119] and others,[109,120] none of these has been found to predispose to alcoholic chronic pancreatitis.

Two clinically distinct pain patterns appear in patients with alcoholic pancreatitis.[2] The first (A type) is characterized by short relapsing pain episodes separated by pain-free episodes, whereas the second (B type) is characterized by prolonged periods of either persistent pain or clusters of recurrent severe pain. A-type pain links recurrent attacks of acute pancreatitis with initiation of the alcoholic chronic pancreatitis.[2,50,121] This apparent relationship between acute alcoholic pancreatitis and chronic pancreatitis continues to be debated.[39,89,122] However, the long-term clinical studies of Ammann et al.,[11,50,121] pathologic studies,[12,13] and observations with hereditary pancreatitis families[19,20] provide strong evidence that recurrent attacks of acute pancreatitis can lead to chronic disease. Indeed, the concept that acute alcoholic pancreatitis reflects the first recognition of underlying chronic pancreatitis appears to be valid in about half of the 247 patients who died of acute alcoholic pancreatitis, but not the other half.[123] Although the mechanisms driving alcoholic chronic pancreatitis remain unproven, we hypothesized that acute attacks of pancreatitis in alcoholics may be a prerequisite to chronic pancreatitis development in some patients.[25,124] However, with our current level of knowledge, it is unclear whether alcoholic chronic pancreatitis represents the dominant cofactor for one or multiple other etiologies and pathways.

Classification of patients with chronic pancreatitis associated with alcohol consumption represents a major problem. Although toxic-metabolic factors likely contribute to disease, the role of genetic factors, recurrent and severe acute alcoholic pancreatitis, or other factors are yet to be determined. Further research will be needed to determine whether A-type pain patterns lead to B-type pain patterns or whether they reflect independent pathways. Furthermore, issues of susceptibility to chronic pancreatitis after low-dose vs. high-dose alcohol

consumption or rapid progression vs. slow progression must be addressed.

Tobacco smoking. Several epidemiologic studies (but not all[125]) uncovered the independent effects of tobacco smoking on the development of chronic pancreatitis.[126–129] The odds ratio for smokers developing chronic pancreatitis compared with nonsmokers ranges from 7.8 to 17.3,[127,128] and the risk increases with the amount of smoking.[128] Furthermore, smoking and alcohol seem to be independent risk factors for chronic pancreatitis.[128] In a French study, smoking was associated with chronic pancreatitis but not alcoholic cirrhosis.[129] The same was true for native American Indians in whom smoking increased the risk of alcoholic chronic pancreatitis but not cirrhosis in men, but not women.[130] These data suggest that smoking may confer specific effects on the pancreas compared with the liver. Although the mechanism is unknown, it is interesting to note that tobacco smoking inhibits pancreatic bicarbonate secretion in humans[131] and reduces both serum trypsin inhibitory capacity and α_1-antitrypsin levels.[132] Thus, tobacco smoking should be considered an independent risk factor for the development of chronic pancreatitis.

Hypercalcemia. Hypercalcemia is associated with acute pancreatitis, possibly through trypsinogen activation[133] and trypsin stabilization.[95,134,135] The relationship between hypercalcemia and pancreatitis became apparent in 1957 when Cope et al.[136] suggested that pancreatitis may be a diagnostic clue to hyperparathyroidism. Shortly thereafter, the relationship between familial hyperparathyroidism and chronic pancreatitis was noted because 3 of 9 family members with hyperparathyroidism had chronic pancreatitis.[137] This relationship has been questioned by some[138] and verified by others,[139,140] but is now an accepted etiology.[15,16,100,141]

Hyperlipidemia. Controversy exists as to the relationship between hyperlipidemia and chronic pancreatitis. Hyperlipidemia causes acute pancreatitis but has rarely been linked with chronic pancreatitis, where it has been listed as a predisposing factor in a few percent of patients with chronic pancreatitis.[15] Further discussion of hyperlipidemia is addressed later in this report.

Medications. In 1981, Ammann et al.[142] reported 4 cases of patients with phenacetin use, renal failure, and chronic pancreatitis. Since this initial report, little has been published on associations between medications and chronic pancreatitis. Furthermore, the effects of phenacetin on the pancreas have never been distinguished from the effects of renal failure.[143]

Toxins. Few toxins have been identified that target the pancreas and predispose to chronic pancreatitis.

Organotin compounds have been suspected of causing chronic pancreatitis in humans.[144] Indeed, in the laboratory di-*n*-butyltin dichloride (DBTC) causes toxic necrosis of the biliopancreatic duct epithelium in rats, leading to duct obstruction and interstitial pancreatitis followed by periductal and interstitial fibrosis.[144,145] In addition to fibrosis, these rats maintain an active inflammatory process within the pancreas that is characteristic of many aspects of human chronic pancreatitis.[146,147] Whether this represents a widespread risk of chronic pancreatitis is unknown.

Chronic renal failure. More than 200,000 patients are currently receiving dialysis, and many of them suffer from a broad range of gastrointestinal complaints.[148] Renal failure is associated with increased rates of both acute[149,150] and chronic pancreatitis.[143,151,152] Both morphologic and functional abnormalities have been noted in various series[143,151,152] (e.g., Figure 4). Although uremic toxins may be directly responsible for some of the histologic changes observed,[153] alterations in gastrointestinal hormone profiles and regulation of bicarbonate and protein secretion may also be important contributors.[148,154,155] Lerch et al.[143] conducted a prospective screening study of 96 outpatients from a chronic ambulatory hemodialysis program using abdominal ultrasonography. Of the patients with chronic renal failure, 20.6% had morphologic alterations of the pancreas compared with 4.7% of controls. The changes in the pancreas of a rat model of chronic renal insufficiency revealed morphologic and biochemical changes in early uremic pancreatic disease that were quite distinct, and corresponded with toxic damage to the pancreas.[153] Further investigation is required to understand the importance of these findings.

Idiopathic Chronic Pancreatitis

The category of idiopathic chronic pancreatitis includes a number of well-described syndromes as well as patients in whom no associated factor can be identified. As new genetic factors, environmental factors, and metabolic factors are identified, and as patients who are misdiagnosed are studied and reclassified, the number of patients in this category will diminish.

Pathology of nonalcoholic chronic pancreatitis. Kloppel and Maillet[12] and Ectors et al.[57] described pathologic studies on 12 patients with nonalcoholic chronic pancreatitis, 4 of them with coexisting autoimmune disorders. The pathologic findings were distinct from those of alcoholic chronic pancreatitis, with predominant T-cell lymphocytic infiltrate around interlobular ducts (especially medium-sized ones), resulting in duct obstruction and occasionally duct destruction, as

well as acinar atrophy and fibrosis. Calcification, pseudocysts, and fat necrosis were not found. This type of pattern was called "chronic duct destructive pancreatitis." Of note, the observed changes in the specimens from patients with autoimmune disorders were identical to those changes seen in the other 8 specimens. This does not mean, however, that the primary cause of all cases of idiopathic chronic pancreatitis is autoimmune.

Early- and late-onset idiopathic chronic pancreatitis. Layer et al.[88] observed that the age of onset of idiopathic pancreatitis is bimodal. In early-onset idiopathic pancreatitis, calcification and exocrine and endocrine insufficiency developed more slowly than in late-onset idiopathic and alcoholic pancreatitis, but pain was more severe. In late-onset idiopathic chronic pancreatitis, pain was absent in 50% of patients. Pfützer et al.[22] recently identified SPINK1 mutations in about 25% of patients with idiopathic chronic pancreatitis (discussed below). Interestingly, 87% of patients with SPINK1 mutations developed pancreatitis before age 20 vs. 64% of SPINK1 mutation–negative patients providing a partial explanation for the bimodal distribution. However, further investigation and validation in other populations is still needed.

Minimum change chronic pancreatitis and "small duct" disease. One of the most hotly debated topics in pancreatology is the syndrome of severe abdominal pain of presumed pancreatic origin with minimal changes on imaging studies. The syndrome is most often seen in middle-aged women. Indeed, many of these patients have reduced pancreatic bicarbonate secretion on functional testing, but (as noted above) pancreatic insufficiency alone is not diagnostic of chronic pancreatitis. Walsh et al.[51] reported on 16 patients (4 men and 12 women) with severe pancreatitis-like pain and normal-appearing pancreata on imaging studies who underwent subtotal (n = 4) or total (n = 12) pancreatectomy.[51] Many pathologic changes were noted, including duct proliferation, duct complex formation, adenomatous nodules, and acinar cell atrophy. However, the significance of these findings was unclear,[51] and too little is known about this problem to make any specific recommendations.

Tropical chronic pancreatitis. Tropical pancreatitis may be referred to as a type of idiopathic chronic pancreatitis occurring in tropical regions. According to its clinical manifestations, an individual with tropical pancreatitis may be subgrouped as either having tropical calcific pancreatitis (TCP) characterized by multiple episodes of severe abdominal pain in childhood, extensive pancreatic calcifications, and signs of pancreatic dysfunction, but no diabetes mellitus at the time of diagnosis, or

fibrocalculous pancreatic diabetes (FCPD) in which diabetes mellitus is the first major clinical sign leading to diagnosis.[156] The etiology of TCP and FCDP remains unknown despite efforts to identify environmental factors or genetic factors such as the PRSS1 R122H mutation,[156] as seen in hereditary pancreatitis.[20] Diet has been excluded as the major etiologic factor, and several lines of evidence suggest that genetic factors may be important (unpublished observation). Major insights into the two forms of tropical pancreatitis are likely in the near future.

Genetic Predispositions to Chronic Pancreatitis

A genetic predisposition to chronic pancreatitis in some families was recognized by Comfort et al.[157] as early as 1952. The 1996 discovery that mutations in cationic trypsinogen gene (UniGene name: protease, serine, 1; PRSS1) cause hereditary pancreatitis[20] opened a new chapter in the book on chronic pancreatitis. The recognition of frequent CFTR mutations[23,158] and serine protease inhibitor, Kazal type 1 (SPINK1) mutations[21,22] in patients with idiopathic chronic pancreatitis has heightened awareness of the importance of genetic mutations in the disease. These discoveries not only provide insights into the molecular mechanisms of pancreatitis, but present the possibility of powerful diagnostic tools.

There are several reasons why we believe molecular and genetic analyses will become important in the future for evaluation of pancreatic disease. First, identification of key mutations in pancreatitis-associated genes will provide important information on risk of developing pancreatitis. Second, mutation detection will assist in early diagnosis of pancreatic disease. Third, mutation identification will help determine the etiology of pancreatitis and provide rational classification. Fourth, molecular classification of pancreatic disorders will help clarify patterns of disease progression and prognosis. Fifth, identifying specific mutations will help us understand gene-environmental interactions. Sixth, knowledge of functional consequence of gene defects may help in developing new therapeutic interventions. Finally, identification of a gene mutation is already important for many patients who are seeking some answers to the question of "why" they have pancreatitis, and to help in family planning decisions and other life issues.

Autosomal dominant disorders: cationic trypsinogen gene mutations. Cationic trypsinogen (UniGene name: protease, serine 1; PRSS1) is among the most abundant molecules produced by pancreatic acinar cells.[159] Cationic trypsinogen plays a central role in hydrolyzing dietary proteins at lysine and arginine amino acid residues and also plays the key role in activating all

other digestive proenzymes.[159] Premature activation of trypsinogen within the pancreas, with subsequent activation of other enzymes leading to pancreatic autodigestion, is believed to be central to the development of acute pancreatitis. Recurrent attacks of acute pancreatitis, as in hereditary pancreatitis, eventually lead to chronic pancreatitis.

Mutations in codons 29 (exon 2) and 122 (exon 3) of the cationic trypsinogen gene cause autosomal dominant forms of hereditary pancreatitis.[19,20,25,26] The codon 122 mutations usually result in a R122H substitution (older nomenclature R117H[26,160,161]), which eliminates a fail-

safe trypsin hydrolysis site in the side chain of trypsin that connects the two halves of the molecule (Figure 8). Elimination of this site causes a gain-of-function mutation because prematurely activated trypsin cannot be inactivated by autolysis.[20,25,162] The N29I mutation (older nomenclature N21I) causes a clinical syndrome identical to the R122H mutation syndrome, although the molecular mechanism causing the gain of function continues to be debated.[25,163] Other less common mutations at codon 29 and 122 have also been identified.[164] The common N29I and R122H mutations occur in patients from the North America,[19,20] Europe,[165–167] Japan,[168] and likely elsewhere. The prevalence of cationic trypsinogen mutations in various populations varies widely, ranging from 0% to 19% among patients presumed to have idiopathic chronic pancreatitis.[118,167,169,170] This observation may reflect the settlement patterns of the descendants of early disease founders.

Mutations at codons 16, 22, and 23 in exon 2 of cationic trypsinogen appear in some patients, resulting in A16V,[160,171,172] D22G,[173] and K23R[166] amino acid substitutions. The D22G and K23R mutations appear to be gain-of-function mutations by facilitating activation of trypsinogen to trypsin.[173] They do not result in the high-penetrance, autosomal dominant pancreatitis as seen with codon 29 and 122 mutations. Indeed, to our knowledge, only 2 patients with chronic pancreatitis and D22G mutation[173] and 1 or 2 patients with chronic pancreatitis and a K23R mutation[166] have been identified and confirmed worldwide. The reason for the low incidence of pancreatitis in patients with activation-facilitating mutations may be because the highly effective fail-safe R122 autolysis mechanism remains intact.
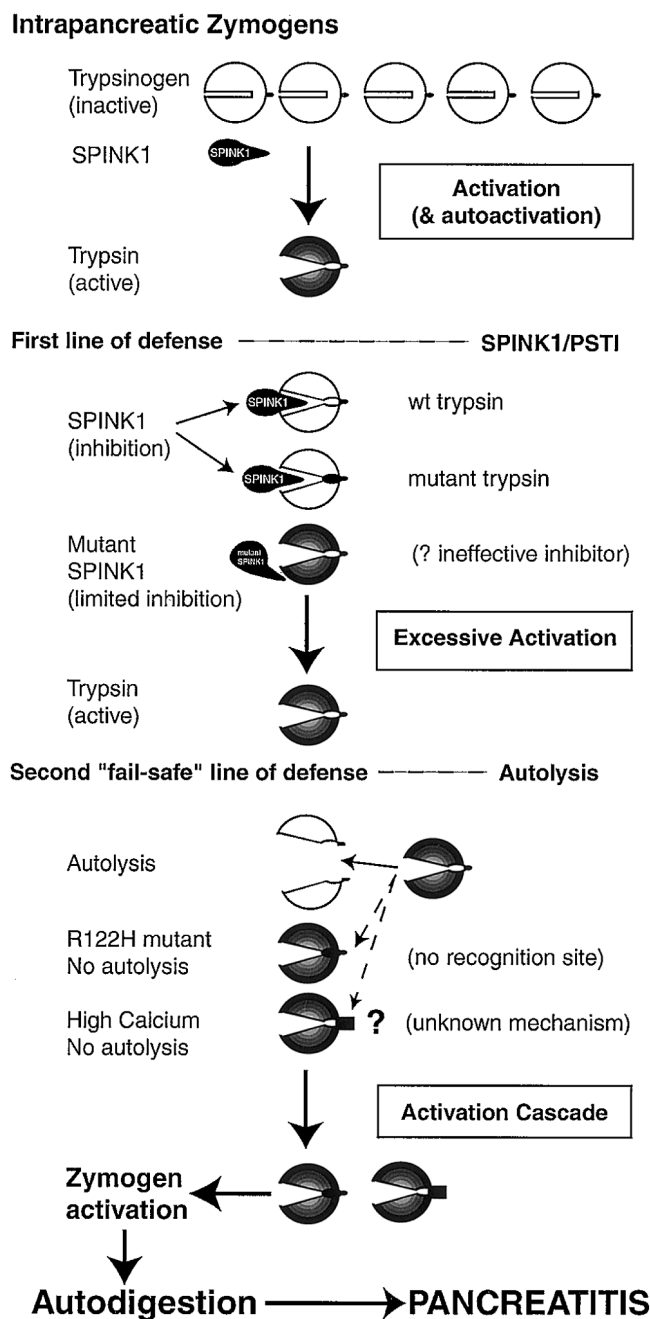

Intrapancreatic Zymogens

Trypsinogen (inactive)

SPINK1

Trypsin (active)

Activation (& autoactivation)

First line of defense ———————— SPINK1/PSTI

SPINK1 (inhibition)

wt trypsin

mutant trypsin

Mutant SPINK1 (limited inhibition)

(? ineffective inhibitor)

Trypsin (active)

Excessive Activation

Second "fail-safe" line of defense ————— Autolysis

Autolysis

R122H mutant No autolysis

(no recognition site)

High Calcium No autolysis

? (unknown mechanism)

Zymogen activation

Activation Cascade

Autodigestion ⟶ PANCREATITIS

Figure 8. Mechanistic model of trypsinogen activation and inactivation within the pancreas. Trypsinogen (inactive) and SPINK1 (also known as pancreatic secretory trypsin inhibitor, PSTI) are synthesized together within the pancreatic acinar cells at a 5-to-1 ratio (*top*). Trypsinogen activation occurs within the acinar cell and threatens to initiate the zymogen activation cascade leading to pancreatic autodigestion and pancreatitis. The first line of defense is trypsin inhibition by SPINK1/PSTI. SPINK1 effectively inhibits up to 20% of potential trypsin (including mutant trypsin). If there is excessive trypsin activation (>20%) or ineffective inhibition by mutant SPINK1, then free trypsin activity increases and again threatens to initiate the activation cascade. The second line of defense is trypsin autolysis. This process begins with hydrolysis of the side chain connecting the 2 globular domains of trypsin at arginine 117 (R117 using the chymotrypsinogen numbering system[26]) coded for by codon 122 (R122 using the codon numbering system[161]). Autolysis fails in hereditary pancreatitis with R122H mutation and possibly others, or under high-calcium conditions. As free trypsin levels increase, the zymogen activation cascade is activated, leading to pancreatic autodigestion and acute pancreatitis. In hereditary pancreatitis and possibly other conditions, repeated attacks of acute pancreatitis lead to chronic pancreatitis.[19] wt, wild type.

The pancreatitis-predisposing mechanism of the A16V mutation remains unknown. However, more than a dozen patients with the A16V mutation and chronic pancreatitis have been reported.[160,171,172]

Genetic testing for cationic trypsinogen mutations in patients. Before clinicians order any test, they must determine the purpose for testing, have the experience to understand and interpret the test results, and anticipate how the results will guide patient management. This is especially true for genetic testing because a genetic test result remains unchanged throughout the life of the patient, has implications for future descendants and other family members, and may impact social and reproductive choices, employment, and insurability.[174–176] Thus, the clinician must understand the implications of testing, be prepared to provide pretest and posttest counseling to the patient (or refer the patient to a genetic counselor), and insure that informed consent is obtained before testing (see recent review[174]).

Clinical and research testing is available for the major cationic trypsinogen mutations (e.g., A16V, K23R, N29I, and R122H through the University of Pittsburgh, Department of Pathology, Molecular Diagnostics Laboratory or through the MMPSG Hereditary Pancreatitis study[20,177] at the University of Pittsburgh, Pittsburgh, PA). Genetic testing falls under class I Food and Drug Administration regulations. Indeed, the protocol of genetic testing must follow the guidelines of several regulatory agencies and be performed in a laboratory with a Clinical Laboratory Improvement Act (CLIA) license.[174,176] In compliance with federal regulations, the results from our own research laboratory are confidentially confirmed in a CLIA-licensed laboratory before any results are disclosed to participants.[175]

In general, the indications for clinical genetic testing vary widely depending on the severity of the disease, the age of onset, the availability of surrogate markers, and the possibility of an effective intervention. Patients are also likely to have their own reasons to pursue genetic testing. Reasons for cationic trypsinogen mutation testing also vary (Table 5) but generally include verification of a clinical suspicion, to help patients understand or

Table 5. Applications for Genetic Testing for Hereditary Pancreatitis

To distinguish a hereditary form of pancreatitis from other causes
To validate patient's symptoms
To expedite diagnosis in children and reduce medical evaluations
To ascertain risk in other relatives
To practice preventive medicine: changing lifestyle to reduce risk for future pancreatic disease

Data from Applebaum et al.[174]

validate their condition, and to assist individuals at risk of pancreatitis (and eventually pancreatic cancer[7]) in making life decisions to minimize risk of disease (e.g., reproduction, diet, smoking).[174] Indeed, identification of an established pancreatitis-associated gene mutation can be valuable in expediting an expensive and prolonged evaluation of recurrent pancreatitis in children, and precludes further evaluation of elusive causes of pancreatitis in adults (e.g., sphincter of Oddi dysfunction or issues surrounding suspicion of alcohol abuse).

The positive and negative predictive value of a genetic test in identifying specific mutations is almost perfect with properly applied modern techniques. The pretest probability of a positive cationic trypsinogen mutation test depends on several factors. The strongest predictors of a genetic etiology are a typical family history (autosomal dominant inheritance pattern) and an early age of symptom onset. However, many patients are unaware of their family histories, have few relatives, may have immediate ancestors who are unaffected, or the etiology of abdominal pain in previous generations was not diagnosed (unpublished observations). Also, an older age of symptom onset (e.g., >20 years of age) does not preclude the diagnosis of a positive test. Although 93% of patients in the MMPSG-Pittsburgh study developed symptoms by the age of 30,[174] only 40% of affected persons from the European Genetic Register of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) study manifested symptoms by the age of 30.[174] This raises the question of selection and/or recruitment bias for studies that were designed for purposes other than determining age of symptom onset and increases the likelihood of a positive result in a patient with symptom onset that occurs later in life.

Interpretation of test results and explanation of their meaning to the patient continues to be a central issue because the test result has implications for the patient as well as the patient's extended family. In general, 80% of individuals with either the R122H or N29I mutation develop at least one episode of acute pancreatitis (i.e., 80% disease penetrance).[178–181] About half of clinically affected individuals with either the R122H or N29I mutation will progress to symptomatic chronic pancreatitis (unpublished observation and Paolini et al.[1]). Furthermore, patients with hereditary pancreatitis face an increased risk of eventually developing pancreatic cancer.[7] Finally, the mutation-positive individual has a 50% chance to pass on the mutation to each child. A positive test result in an unaffected person is interpreted as an increased risk of pancreatitis, with this risk possibly diminishing with age. A negative test result in a family

with a known mutation essentially eliminates the risk of developing this genetic form of pancreatitis. If a mutation has not been previously identified in the family, then a negative test result in an unaffected person is considered noninformative because one cannot distinguish whether the tested individual is free from genetic risk or whether he/she has inherited a different pancreatitis-predisposing gene mutation.

A primary concern of patients undergoing genetic testing for hereditary pancreatitis is insurance discrimination.[175] Participating in a research study, rather than going through a clinical laboratory, is attractive to patients who do not want their test results available as part of their medical record. In these cases, the results are disclosed directly to the patient. The patient then may decide to whom they will disclose the results.

The genetic testing of children warrants additional consideration. Unlike an adult patient, a child legally cannot provide informed consent. Thus, the decision for a child is essentially left to the parents or legal guardian. For children 7 years of age and older, a parent or legal guardian may provide consent for genetic testing, although these older children should provide assent or agreement to the testing.[182–184] The primary reason for testing of children for cationic trypsinogen gene mutations is to assist in determining the cause of unexplained pancreatitis or to confirm suspected pancreatitis in a child at risk of hereditary pancreatitis, thereby limiting further investigations. The testing of purely asymptomatic children is strongly discouraged because currently there is no clear medical benefit in identifying carriers at a young age.[174,185] Testing for the purpose of intervention with diet, medication, or surveillance for complications of a genetic disorder (e.g., undertaking repeated colonoscopies for patients with the familial adenomatous polyposis syndrome) has been advocated.[185] Because alcohol, emotional stress, and fatty foods have been reported to precipitate pancreatitis attacks[178] and smoking increases the risk of both pancreatitis[126–128] and pancreatic cancer,[5,186,187] testing for the purpose of encouraging mutation-positive older children to avoid these excesses could be considered justifiable. However, it has also been argued that avoidance of fatty foods, alcohol, and tobacco represents excellent general advice for all children and therefore provides no compelling reason for testing.[174] In either case, the personal desires of older children to postpone testing or to proceed with testing to relieve their own anxieties and learn more about their own personal health must also be carefully considered.[184] Finally, ownership of test results in children must be addressed. When parents provide consent for their chil-

dren, they also take ownership of their children's results. In some cases, children may not wish to learn their test results. When a child and his/her parents are not in agreement with the decision to learn the test results, testing should be postponed. A recent study by O'Connell,[184] however, suggests that parents who had their children tested for trypsinogen mutation were generally motivated by legitimate concerns and for the welfare of their child. Interestingly, parents preferred to disclose the test results personally to their affected child, and did so in an age-appropriate manner with the purpose of explaining the cause of their child's symptoms, to help the child adjust to their gene status, and to help the child pay closer attention to any "stomach" problems.[184]

No specific treatment exists for the prevention or treatment of chronic pancreatitis. However, some patients report that vitamins, antioxidants, or digestive enzyme supplements are helpful (personal observation), and therefore we do not discourage their use.[188] Symptomatic treatment for pancreatic duct obstruction or other sources of pain should be handled in a manner similar to other forms of pancreatitis.[3] Stronger recommendations for specific treatments await clinical evidence from well-designed trials.[188] Finally, there is an increased risk for the development of pancreatic cancer with long-standing chronic pancreatitis from any cause,[6] but especially hereditary pancreatitis.[7] Unfortunately, no good screening test exists for the early diagnosis of pancreatic cancer in high-risk groups,[189,190] and prophylactic pancreatectomy cannot yet be advocated.

Autosomal Recessive/Modifier Genes

CFTR mutations. Cystic fibrosis (CF) is a common autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR).[191] Major mutations in both alleles result in the commonly recognized CF clinical features of abnormal sweat chloride concentrations, neonatal hypertrypsinogenemia, pancreatic pseudocysts formation, and fibrosis (i.e. "cystic fibrosis") with clinical chronic pancreatitis, and progressive pulmonary disease. Among CF patients, 66% have a 3–base pair deletion of the phenylalanine-coding codon 508 (ΔF508), although approximately 900 other mutations have been reported.[192,193] Most CFTR mutations can be classified into 1 of 5 severity categories based on the demonstrated or presumed molecular consequences.[194,195] Typical CF patients with pancreatic insufficiency tend to have two severe mutations (i.e., class I, II, or III), whereas CF patients with pancreatic sufficiency from birth tend to have at least one CF "mild allele" (i.e., class IV or V).[195]

In 1998, 2 groups reported that a significant association between patients with idiopathic chronic pancreatitis and various CFTR mutations.[23,24] Indeed, several mild, "pancreas-sufficient" mutations (e.g., CFTR R117H and the intron 8 "5T allele," which results 80% reduction of exon 9 expression[196,197]) seem to be associated with idiopathic chronic pancreatitis[23,24] as well as another feature of CF, congenital bilateral absence of the vas deferens (CBAVD).[196,198] Other mild CFTR mutations (e.g., L997F[199]) may also be associated with neonatal hypertrypsinemia and/or idiopathic pancreatitis, but not lung disease or an abnormal sweat chloride. Although initial reports suggested that idiopathic chronic pancreatitis was associated with a single allelic mutation of CFTR, more recent evidence suggest that patients with chronic pancreatitis may actually have compound heterozygous mutations of CFTR and mild CF because they also have abnormal nasal bioelectrical responses that accurately identifies abnormal CFTR function.[200] Thus, a subset of patients with idiopathic chronic pancreatitis have a variety of CFTR mutations without other features of CF.

Genetic testing for CFTR mutations. CFTR is a large molecule with 1480 amino acids, coded for by more than 4400 nucleotides in 24 exons.[191] Furthermore, development of pancreatitis in these patients appears to be associated with loss of CFTR function so that many combinations of CFTR mutations must be considered. This makes mutational screening of the entire CFTR gene difficult and very expensive, thereby limiting this approach to specialized research laboratories. Some commercial laboratories do offer clinical testing for a panel of mutations commonly associated with CF. Unfortunately, these panels may not include many of the "mild" CFTR mutations associated with pancreatitis.[200] Furthermore, because CFTR mutations are common in the population, the identification of one polymorphism does not alone prove that this is the cause of pancreatitis, nor does the identification of a CFTR polymorphism in asymptomatic individuals mean that they are at high risk of pancreatitis (e.g., if the incidence of pancreatitis is 1/16000[100] and a CFTR R117H genotype increased the risk 2.6-fold,[200] the overall risk becomes 2.6/16000 or 0.16%). Therefore, Cohn et al.[200] suggest that, presently, CFTR testing might be considered for individuals in whom pancreatitis appears to be the earliest manifestations of classic CF, or in young patients with pancreatitis and borderline sweat chloride values for the purposes of referring these individuals to CF centers or for family planning. As continued research efforts clarify the role of CFTR mutations in pancreatic disease, clearer guidelines for testing and patient management will emerge.

SPINK1 (PSTI) Mutations

Pancreatic secretory trypsin inhibitor (PSTI, UniGene name: serine protease inhibitor, Kazal type 1; SPINK1) is a 56–amino acid peptide that specifically inhibits trypsin by physically blocking the active site. SPINK1 is synthesized by pancreatic acinar cells along with trypsinogen, and it colocalizes with trypsinogen in the zymogen granules. In the mechanistic models of pancreatic acinar cell protection, SPINK1 acts as the first line of defense against prematurely activated trypsinogen in the acinar cell.[20–22,159,201] However, because of a 1:5 stoichiometric disequilibrium between SPINK1 and trypsinogen,[159] SPINK1 is only capable of inhibiting about 20% of potential trypsin. Thus, within the pancreas SPINK1 appears to act as the first line of defense against prematurely activated trypsinogen.

Because gain-of-function trypsin mutations cause acute pancreatitis and chronic pancreatitis, it was hypothesized that loss of trypsin inhibitor function would have similar effects. In 2000, the role of SPINK1 mutations in chronic pancreatitis emerged.[21,22,202] SPINK1 N34S and P55S mutations are relatively common, being present in ~1% of alleles tested and therefore ~2% of the general population.[22,202] Families affected with pancreatitis in whom trypsinogen mutations were excluded often have SPINK1 mutations, but the mutations do not segregate with the disease.[22,202] Thus, SPINK1 mutations are not sufficient to cause hereditary pancreatitis in an autosomal dominant inheritance pattern. However, the frequency of SPINK1 mutations in populations with idiopathic chronic pancreatitis is markedly increased (23% to ~25%),[21,22] proving that these mutations are clearly associated with pancreatitis. Interestingly, chronic pancreatitis occurred with heterozygous, compound heterozygous or homozygous genotypes,[21,22] and the severity of pancreatitis or age of disease onset among genotypes is similar.[22] Furthermore, because SPINK1 N34S and P55S mutations are common in the general population (~2%) and idiopathic chronic pancreatitis is rare, the risk of an asymptomatic SPINK1 mutation carrier developing chronic pancreatitis is low (~1%, given the observed frequency for N34S mutations and a population prevalence for idiopathic chronic pancreatitis of ~1/16,000[100]). Thus, the disease mechanism is more complex than a simple autosomal recessive one.

SPINK1 mutations appear to act as disease modifiers,[22] lowering the threshold for initiating pancreatitis or possibly worsening the severity of pancreatitis caused by other genetic and/or environmental factors. In our

mechanistic model (Figure 8), SPINK1 represents the first line of defense against prematurely activated trypsinogen within the pancreas.[20–22,159] If the SPINK1 N34S and other mutations cause SPINK1 loss of function,[22] then the model would predict that the levels of active trypsin within the pancreas would increase above normal basal levels. However, if the trypsin R122 side-chain autolysis mechanism remains intact (above), the pathophysiologic activation process would typically fail to progress beyond the fail-safe trypsin autolysis phase. If so, only patients with inherited or acquired deficiencies or impairments of other pancreatic protective mechanisms would develop pancreatitis.

Genetic testing for SPINK1 mutations. With the discovery of a new disease-associated mutation, the question of presymptomatic and symptomatic testing quickly arises. Testing for SPINK1 mutations in individuals with early chronic pancreatitis may provide important information on predisposing causes of pancreatitis for the concerned patient. But because less than 1% of patients with a heterozygous SPINK1 mutation alone are likely to develop pancreatitis, there is no reason to do presymptomatic testing. SPINK1 mutation do appear to be predictive of earlier age of onset of symptoms than idiopathic chronic pancreatitis, so that testing is unlikely to be positive in patients who develop pancreatitis after age 20.

α_1-Antitrypsin gene polymorphisms. In symptomatic patients, SPINK1 gene mutation testing may be as informative as cationic trysinogen gene mutation testing. α_1-Antitrypsin deficiency was reported to be associated with chronic pancreatitis by 2 groups in the 1970s.[203,204] However, this observation has not been confirmed in independent populations of (predominantly) alcoholic patients.[15,109,205] Also, the possibility that the decreased α_1-antitrypsin was actually caused by tobacco smoking[132] has not been excluded. Additional testing in other populations, especially in patients with idiopathic chronic pancreatitis, should be considered.

Autoimmune Chronic Pancreatitis

Autoimmune chronic pancreatitis is a distinct entity with characteristic histologic, morphologic, and clinical features. Features of autoimmune pancreatitis such as hypergammaglobulinemia have been recognized for more than 35 years.[206] Autoimmune pancreatitis may be isolated or occasionally observed in association with the Sjögren syndrome,[57,207] primary biliary cirrhosis,[207] primary sclerosing cholangitis,[57,208–210] Crohn's disease and ulcerative colitis,[57,211] or other immune-mediated disorders.

Histologically, the ductal lesions in the pancreas resemble those seen in the salivary glands involved in autoimmune sialadenitis with destruction of the duct and fibrosis atrophy of the acinar tissue without calcifications.[12] Another histologic study of patients with non-alcoholic pancreatitis with or without other autoimmune diseases by Ectors et al.[57] noted a unique pattern of pancreatic inflammation, particularly involved the ducts and resulting in duct obstruction and occasionally duct destruction. Furukawa et al.[65] described 3 patients with autoimmune pancreatitis evaluated by percutaneous needle biopsy of the pancreas. In each case, histopathologic examination revealed lymphocytic infiltration, plasma cells, and fibrosis.

Imaging studies may also help to identify autoimmune pancreatitis.[65,212] On CT or ultrasound examination, the pancreas appears diffusely enlarged with poor or delayed contrast enhancement.[65,212,213] Irie et al.[212] also noted that on CT, autoimmune pancreatitis appears with a capsule-like rim, which is thought to correspond to an inflammatory process involving peripancreatic tissues. MRI examination may reveal diffuse pancreatic enlargement with hypointensity on T1-weighted images, and ERP may show diffuse narrowing of the main pancreatic duct with an irregular wall.[65,213]

Recently, autoantibody profiles of autoimmune pancreatitis have been reported.[214] Multiple autoantibodies were observed in 17 of 17 patients, including antinuclear antibodies (13/17), antilactoferrin antibodies (13/17), anti–carbonic anhydrase II antibodies (10/17), rheumatoid factor (5/17), and anti–smooth muscle antibodies (3/17) but not antimitochondrial antibodies. CD8- and CD4-positive cell numbers were also increased in the peripheral blood, suggesting a Th1-type immune response.[214]

Autoimmune chronic pancreatitis therefore represents a distinct form of chronic pancreatitis. This diagnosis is important to make because these patients appear to respond promptly to oral steroid therapy.[65,213,214]

Recurrent and Severe Acute Pancreatitis

Although historically controversial, the association between recurrent acute and chronic pancreatitis has been established by careful clinicopathologic studies,[50] pathologic arguments,[12,13] some animal work,[215] and hereditary pancreatitis.[19,20] Furthermore, clinical studies have demonstrated that recovery from acute pancreatitis may not always be complete,[216] requiring the etiology of some cases of chronic pancreatitis to be classified as recurrent and severe acute pancreatitis. Hereditary pancreatitis begins as recurrent acute pancreatitis, and is discussed above under genetic etiologies. A subset of patients with recurrent acute alcoholic pancreatitis develop chronic pancreatitis and could possibly be classified as having recurrent and severe pancreatitis (discussed

above). Several disorders characterized as causing acute pancreatitis may, in some cases, progress to chronic pancreatitis. Gallstone-associated pancreatitis remains controversial. Although gallstones were the only finding in 17 of 462 patients with chronic pancreatitis in one series, they were not thought to be causative of chronic pancreatitis.[16] The example of hyperlipidemia is presented.

Recurrent acute pancreatitis from hyperlipidemia. Although hypertriglyceridemia (e.g., >500 mg/dL[217]) is associated with recurrent acute pancreatitis, the relationship between hypertriglyceridemia or other hyperlipidemias and chronic pancreatitis remains controversial. Evidence to consider includes familial lipoprotein lipase deficiency[218,219] and apolipoprotein C-II deficiency,[220,221] which both cause chronic hypertriglyceridemia and bouts of pancreatitis that segregate with the disease gene. Chronic pancreatitis was observed in an extended Dutch kindred[222] with genetically deficient lipoprotein lipase catalytic activity who had recurrent acute pancreatitis and, in at least 3 family members, documented chronic pancreatitis. Chronic pancreatitis was not recognized in the kindred with lipoprotein lipase deficiency reported by Wilson et al.[218] Cox et al.[220] reported a kindred with apolipoprotein C II deficiency with recurrent pancreatitis and chronic pancreatitis, although "chronic pancreatitis" was not defined (i.e., 1 of 5 pancreatitis patients had "malabsorption syndrome" and diabetes). One of 3 patients with apolipoprotein C-II deficiency syndrome reported by Beil et al.[221] had pancreatic calcifications. DiMagno et al.[16] noted that 5 of 462 patients evaluated for chronic pancreatitis had pre-existing hyperlipidemia (their Table 2), but hyperlipidemia was not listed as an etiology of chronic pancreatitis (their Table 1). Clinical series[217] and reviews[100,223] of this topic generally recognize only acute pancreatitis with hypertriglyceridemia or do not discuss this issue,[15] whereas others note that familial chylomicronemia syndromes lead to severe pancreatic insufficiency.[219] Taken together, it appears that in the most severe, prolonged, and poorly controlled cases of hyperlipidemia (e.g., genetic lipoprotein lipase deficiencies) dominated by with recurrent acute pancreatitis, chronic pancreatitis can develop. However, this appears to be rare.

The important consideration for patients diagnosed with recurrent and severe acute pancreatitis associated chronic pancreatitis is etiology. For evaluation of recurrent acute pancreatitis the reader is referred to Somogyi et al.[69]

Obstructive Chronic Pancreatitis

Obstructive chronic pancreatitis is a distinct morphologic form of chronic pancreatitis associated with pancreatic duct dilation proximal to the obstruction, atrophy of acinar cells, and a uniform diffuse fibrosis replacing the pancreatic parenchyma.[224] It is a pathologically distinct form of pancreatitis.[12] A number of entities have been associated with obstructive chronic pancreatitis, including sequelae of acute pancreatitis, trauma, tumor, sphincter of Oddi dysfunction, and pancreas divisum.[225–228] The histologic and functional changes associated with this form of chronic pancreatitis may be partially or fully reversible if the obstructive process is treated early enough.[224]

Sphincter of Oddi dysfunction. Sphincter of Oddi dysfunction (SOD) refers to the benign, noncalculous obstruction to flow of bile or pancreatic juice.[229] "Dysfunction" can be subdivided into patients with stenosis and those with dyskinesia, although clinically the 2 groups behave quite similarly. The resulting ductal hypertension from either subgroup is thought to be the mechanism associated with the clinical signs and symptoms (pain, biliary duct dilation, abnormalities in liver enzymes) and the associated pancreatitis. Close to 60% of patients with "idiopathic recurrent pancreatitis" have demonstrated manometric abnormalities consistent with SOD.[229] In addition, at least one report suggests an association between SOD and chronic pancreatitis.[228] Because SOD has a number of potential treatment options, SOD as a cause of chronic pancreatitis will be an important area for further investigation, because patients may have the option of being identified and treated at an early stage. Of note, the family reported by Robechek[230] characterized with sphincter hypertrophy, chronic pancreatitis, and pain relief with surgical sphincteroplasty was later determined, by our group, to have cationic trypsinogen N21I mutations[19] (now numbered as N29I[26,160,161]). This raises the question of whether SOD is a primary or secondary finding in some cases. Regardless of origin, sphincteroplasty or sphincterotomy offer symptomatic relief in some patients.[230]

The categorization of patients with chronic pancreatitis according to the factor most strongly associated with chronic pancreatitis (Table 3) rather than by the severity of disease (Table 1) is an important step for clinical understand and research aspects of pancreatic diseases. Improvements in data organization and proper categorization of patients will assist in identifying additional predisposing genetic and environmental factors, and allow for the design of patient-specific treatment pro-

grams. Furthermore, the clinical course and outcome of treatment interventions can be more clearly determined.

Staging of Chronic Pancreatitis

The staging of chronic pancreatitis can be accomplished by pathologic,[11] functional,[11,82] or structural[37,38] evaluation. Staging the severity of pancreatitis is usually rather coarse, generally being divided into mild, moderate, and severe categories. New, simple, and accurate function tests are still needed.

Invasive assessment of function is very infrequently done in the United States. Invasive testing involves an experienced person passing an oroduodenal tube and maintaining correct placement under fluoroscopy followed by bolus infusion of exogenous hormones (e.g., secretin, cholecystokinin) while nonabsorbable markers (e.g., PEG 4000) are infused into the duodenum to accurately calculate secretion volume. Fluid is then continuously aspirated for a prolonged time period to determine bicarbonate concentration and, in some cases, enzyme output. Only 5 centers in the United States perform more than 50 invasive function testing procedures per year, and there is significant variability in the methods that are used and the standards of normal and abnormal.[231] Likewise, in Europe invasive testing is rarely performed to answer clinical questions, even at the major pancreas centers. Direct, (i.e., invasive) testing of pancreatic function remains the gold standard, but less invasive and complicated test are needed.

Many attempts have been made to develop noninvasive pancreatic function tests.[18,86,232–234] The 2 main approaches are to give an oral agent with a meal and then determine rates of hydrolysis and the measurement of digestive enzymes in the stool. No function test is highly sensitive to mild pancreatic dysfunction.

Two indirect tests are briefly considered: the pancreolauryl test and fecal testing of pancreatic elastase 1. The pancreolauryl test measures the hydrolysis of fluorescein dilaurate by arylesterase.[235,236] Although the sensitivity of this test is improved with administration of secretin,[237] it may not be specific for pancreatic disease, and serial examination to stage or follow the clinical course of patients with chronic pancreatitis has not, to our knowledge, been done. Measurement of pancreatic elastase 1 in the stool appears to be the most common indirect screening test for pancreatic insufficiency in Europe, and may soon be available in the United States. The advantages of this test are that pancreatic elastase 1, unlike most other pancreatic enzymes,[238] survives passage through the intestine and is present in stool. It is specific for the pancreas, and, by using a sandwich ELISA technique with 2 monoclonal antibodies (ScheBo Tech, Giessen, Germany), is not affected by ongoing enzyme supplement therapy.[239,240] Disadvantages are that diarrhea may give a falsely low measure (due to dilution) and that it is not highly sensitive and completely specific for milder pancreatic diseases.[241] However, because of its simplicity and sensitivity for moderate to severe pancreatic insufficiency, it is becoming the indirect test of choice.[242] Elastase 1 has not been used to serially measure pancreatic function. Thus, to date, no indirect test of pancreatic function exists for accurate staging of chronic pancreatitis.

Conclusions

Understanding and treating chronic pancreatitis has progressed remarkably over the last 5 years. Clarifying issues of diagnosis, classification, and staging are important and demand further evaluation. For diagnosis, an adequate pancreatic biopsy is the gold standard. Tests, such as a CT scan revealing pancreatic calcifications, dilated main pancreatic duct, and parenchymal atrophy, remain useful because correlation with pancreatic tissue is nearly 100%. Etiology-based classification is important for both clinical and research purposes. The TIGAR-O system is presented as a working example of such a system. The recognition that multiple factors, including genetic, may predispose individuals to chronic pancreatitis further supports general adoption of an etiology-based system. Once the diagnosis of chronic pancreatitis is made and the contributing etiologic factors are determined, accurate staging of chronic pancreatitis becomes important. Unfortunately, current technology and expertise markedly limit this important area. However, recent progress in understanding chronic pancreatitis has been remarkable. The future should be much brighter than the past.

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