



Proposed roles of pancreatic enzymes and other factors in normal pancreatic function compared to the pathogenesis of pancreatitis.

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Diseases of the Pancreas

SUMMARY OF RESEARCH GOALS

The exocrine pancreas, which produces and secretes multiple enzymes necessary for digestive function, is vulnerable to a variety of disorders that, collectively, affect more than 1 million Americans each year. The Commission recommends a series of research goals that are focused on the most prevalent of these disorders—acute and chronic pancreatitis and their sequelae. Pancreatitis can be triggered by many possible causes, including gallstones, alcohol abuse, certain medications, autoimmunity, and diseases such as cystic fibrosis (CF), or it may be of unknown etiology. Research is needed to identify the biologic and genetic factors that increase a person's susceptibility to acute pancreatitis and/or the transition to chronic disease. The development of innovative diagnostic, preventive, and therapeutic approaches to pancreatitis has the potential to reduce the burden of this disease in both children and adults. Equally important is the need to understand the mechanisms of pancreatic pain, a highly prevalent complication of all forms of pancreatitis that is difficult to treat and severely erodes the quality of life of patients with pancreatic disease. Research to understand the risk factors for and mechanisms of progression to pancreatic cancer is particularly critical for patients who develop pancreatitis at a young age and are, therefore, at a corresponding increased lifetime risk for pancreatic cancer.

INTRODUCTION AND BACKGROUND

The pancreas plays a very important role in nutrient absorption via its synthesis of digestive enzymes (e.g., proteases, phosphatases, lipases, amylases, and others). The gland can be afflicted by a surprising diversity of pathologic processes leading to various diseases and clinical syndromes. Disorders of the pancreas affect more than 1 million persons in this country (1.15 million in 1998) and are estimated to result in nearly \$3 billion in annual direct and indirect costs. As a group, there were 277,000 hospitalizations and 475,000 ambulatory care visits due to pancreatic diseases in 2004. Specifically, acute pancreatitis is the commonest cause of hospitalization for pancreas-related disorders in the country, accounting for 254,000 discharges, with a median charge of \$13,435, and resulting in more than 2,800 deaths in 2004. CF, which interferes with pancreas function, is the most common inherited fatal disease in Caucasians, occurring in about 1 in every 3,500 births each year. This burden of disease contrasts with the relatively sparse number of researchers and actively funded proposals in this area.

The most widespread disorders of the pancreas are acute and chronic pancreatitis, or inflammation of the pancreas. In acute pancreatitis, inflammation begins abruptly and either resolves or worsens within days. About 2 percent of acute pancreatitis cases are fatal, often due to complications affecting other organs, such as the lungs, cardiovascular system, or kidneys. The most common causes of acute pancreatitis are gallstones, which traverse the bile duct and may inflame the pancreas by transiently blocking its drainage into the duodenum, and alcohol excess. Other causes include metabolic derangements, such as increased circulating triglycerides, certain medications, and invasive diagnostic tests evaluating the pancreas and bile ducts (e.g., endoscopic retrograde cholangiopancreatography [ERCP]).

The most frequent known cause of chronic pancreatitis is also chronic alcohol abuse. Additional causes include hereditary pancreatitis due to mutations in genes that encode for key pancreatic molecules, such as trypsin or the cystic fibrosis transmembrane conductance regulator (CFTR), abnormalities of which are associated with CF and its variations. In up to 10-20 percent of cases, the cause remains unknown (idiopathic). The most frequent sequelae of chronic pancreatitis are pain, endocrine failure (resulting in diabetes mellitus), and exocrine failure (resulting in fat and protein malabsorption). Pain is present in approximately 75 percent of patients with alcoholic chronic pancreatitis, 50 percent of patients with late-onset idiopathic chronic pancreatitis, and all patients with early-onset idiopathic chronic pancreatitis. Pain is the most difficult symptom of chronic pancreatitis to treat, with many patients facing the prospect of lifelong dependence on narcotics. Our lack of knowledge about what causes pain in pancreatitis has been a serious obstacle to improving the care of these patients, leading to various empiric approaches that are often based on purely anatomical grounds, are generally highly invasive, and are not always effective. Individuals with alcoholic pancreatitis also suffer from issues of addiction to alcohol, smoking, and narcotics, which considerably complicate the care of these patients. Finally, chronic pancreatitis is associated with an increased risk for pancreatic cancer. While relatively uncommon, development of pancreatic cancer can be particularly important in those whose disease begins in childhood, such as patients with hereditary pancreatitis.

With increased use of sophisticated abdominal imaging procedures, such as high-resolution CT scan and MRI, cystic lesions of the pancreas are being recognized, often as incidental findings during investigation for other abdominal complaints. Some of these (pseudocysts) occur in the setting of

pancreatitis and may be a consequence of ductal injury. In the absence of preceding inflammation, these lesions are ominous and often neoplastic in nature. In recent years, advances in the understanding of the pathology of these cystic lesions have led to revision of the classification and nomenclature of these tumors into mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) and its variants. Both MCN and IPMN are mucinous tumors that have potential to turn malignant. While MCNs are frequently found in middle-aged women, IPMN is often seen in the elderly. Since mucinous tumors of the pancreas are precancerous, their discovery is an important health concern. They present great challenges with regard to diagnosis, treatment, and surveillance.

From a pathologic perspective, three distinct precursors to invasive pancreatic cancer have been identified, including: (1) MCNs, (2) IPMNs, and (3) pancreatic intraepithelial neoplasia (PanIN). The first two are macroscopic (i.e., generally visible on imaging techniques), while the third is microscopic in nature. All three pre-malignant processes begin as benign, noninvasive entities and progress through a series of as-yet poorly defined genetic and pathologic changes toward cancer. The link between chronic pancreatitis and pancreatic cancer and the role of PanINs in these diseases are incompletely understood.

The product of the CF gene, CFTR, is important for chloride ion transport on the apical surface of exocrine gland epithelial cells. Mutations in CFTR result in abnormally thick secretions that damage a variety of organs, including the lungs, liver, and pancreas. Pancreatic exocrine failure occurs in 85-90 percent of CF patients and results from blockade of ducts by thick mucus plugs, causing injury and fibrosis. Less frequently, diabetes will also result. In addition to the classic form of CF, patients with milder

variations in the gene encoding CFTR will have residual pancreatic exocrine function, but may be at risk for recurrent pancreatitis.

Although diabetes can be considered a disorder of the pancreas, it is not considered a digestive disease in the strict sense and, although an important component of chronic pancreatitis and pancreatic cancer, will not be discussed in this research plan. Pancreatic cancer, the fourth leading cause of cancer death in the U.S., is included in the chapter on *Cancers of the Digestive System*.

RECENT RESEARCH ADVANCES

Acute pancreatitis

Researchers have recognized clearly that acute pancreatitis can affect the entire body and is associated with a systemic inflammatory response. Organ failure has been found to be a more important determinant of morbidity and mortality than necrosis or other local complications. Other important advances that are still in progress include elucidation of the complex cytokine/chemokine responses in acute pancreatitis, the development of *in vivo* models of acute pancreatitis, and understanding the nature of calcium and other cell signaling processes that mediate the physiologic and pathologic acinar cell responses.

Chronic pancreatitis

Progress has been made in understanding fibrosis events in the pancreas, particularly with regard to the role of stellate cells. With the development of valid animal models to study pancreatic pain, important molecular mechanisms and potential therapeutic targets, such as receptors and ion channels on sensory neurons (e.g., TRPV1), are beginning to be identified.

Genetic mutations and the risk of pancreatitis

Only a small subset (usually less than 5 percent) of patients with known risk factors for pancreatitis (e.g., chronic alcohol abuse or pancreas divisum) develops the disease. However, the genetic basis for this is not understood. Since the discovery in 1996 that mutations in the cationic trypsinogen gene cause hereditary pancreatitis, other genes have been implicated in apparently sporadic pancreatitis, such as recent reports concerning the role of genetic variation in the trypsin-degrading enzyme, chymotrypsin C. The frequent identification of mutations in the *CFTR* gene and the serine protease inhibitor, Kazal type 1 (*SPINK1*) gene in patients with idiopathic chronic pancreatitis and in a small proportion of the healthy population suggests that genetic predisposition may be necessary for development of disease in those with identifiable risk factors.

Recognition of autoimmune pancreatitis (AIP) as a distinct clinical entity

AIP is the pancreatic manifestation of a systemic autoimmune disorder. AIP is a form of chronic pancreatitis distinct from classically described chronic, calcifying pancreatitis. AIP has unique clinical, serologic, morphologic, and histologic features. The most frequently described presentation of AIP is that of a pancreatic mass that mimics pancreatic ductal adenocarcinoma in clinical presentation. If recognized prospectively, the inflammatory mass of AIP responds to steroid therapy, and the need for pancreatic surgery can be avoided. Interestingly, unlike usual chronic pancreatitis, AIP is a relatively painless disease despite histology showing chronic pancreatic inflammation and evidence of pancreatic edema, peripancreatic inflammation, and, in some cases, pancreatic calculi. This phenomenon is highly worthy of further study.

Pancreatic imaging

Advances in endoscopic ultrasound (EUS) technology have improved dramatically the ability to visualize even subtle alterations in pancreatic structure. These changes are visible before traditional cross-sectional imaging techniques (e.g., CT scan) show any abnormality, allowing for the possibility of diagnosing chronic pancreatitis early. However, the capability for high-resolution imaging is also the greatest drawback of this technology. Subtle alterations in structure are seen, for example, in alcoholics without pancreatitis, smokers, the elderly, and after bouts of acute pancreatitis. EUS also provides the opportunity to obtain tissue for histologic diagnosis of chronic pancreatitis without surgical resection of the pancreas.

Cystic lesions of the pancreas

A major boost to the field has come from the World Health Organization classification of cystic disorders of the pancreas, which has distilled many different types of classifications into one that determines whether or not the cells are malignant and whether or not tissue invasion has occurred. This revised system has significantly improved the ability of researchers to coordinate multiple studies. Progress in our understanding of cystic lesions of the pancreas has come from the identification of differences in diagnosis and natural history of MCN from IPMN, as well as the recognition that not all forms of IPMN require operative intervention. In addition, studies have introduced the concept of less aggressive treatment for small (less than 3 cm) cystic lesions in the pancreas. Finally, researchers have gained important new insights into the molecular mechanisms of neoplastic transformation of cystic lesions.

Research Goal 10.1: Determine the biologic factors involved in the pathogenesis of acute pancreatitis, with particular emphasis on the mechanisms of tissue necrosis and systemic complications.

It is unclear why the majority of patients with acute pancreatitis do not develop the systemic inflammatory response syndrome or pancreatic necrosis. However, those who do will have a perilous clinical course, often complicated by organ failure and death. It is critical, therefore, to understand the biologic pathways leading to necrosis following a noxious insult. Such knowledge has the potential to identify novel and effective therapeutic targets, as well as much needed surrogate markers (clinical, hematological, or imaging) for mortality, necrosis, and systemic complications in acute pancreatitis.

Objectives:

- Understand how noxious insults, such as ethanol, gallstones, and others, initiate pancreatic injury and inflammation in adults and children.
- Understand the role of obesity, sphincter of Oddi dysfunction, and anatomic variations of the pancreas in the development of pancreatitis.
- Identify the biologic mechanisms leading to necrosis in acute pancreatitis.
- Understand the biologic mechanisms responsible for post-ERCP pancreatitis.
- Understand the role of specific cytokines and other inflammatory factors, including enteric bacteria and their products, in the development of systemic complications and multi-organ failure.

Research Goal 10.2: Understand the transition from acute to chronic pancreatic injury, particularly with respect to the role of alcohol.

Significant insight has been gained into the mechanisms by which alcohol or other insults lead to acute cellular injury. However, how these events lead to chronic inflammation and fibrosis or endocrine and exocrine cell loss remains unknown. These questions are of great clinical relevance given how often chronic pancreatitis is accompanied by enzyme insufficiency leading to malabsorption and insulin deficiency leading to diabetes.

Objectives:

- Understand how ethanol, smoking, and other putative etiologic factors contribute to chronic injury.
- Determine the biology of pancreatic fibrosis and chronic injury, including the role of stellate cells and other co-factors.
- Understand the nature and mechanism of endocrine cell loss in chronic pancreatitis.
- Understand the mechanisms of parenchymal and islet cell regeneration in response to chronic injury.
- Understand the biologic nature and importance of islet-pancreatic communication in the pancreas.

Research Goal 10.3: Understand genetic factors and their interactions with exogenous insults, with respect to pathogenesis, complications, and natural history of pancreatitis and other pancreatic disorders.

It is clear that host factors, including genetic variability, have a major influence in determining the risk for inflammation and subsequent clinical phenotype after insults, such as excessive alcohol use. Knowledge of these specific factors will be valuable in risk stratification and development of effective measures for prevention of disease. In addition, identification of these genes will provide crucial insight into the molecular mechanisms underlying pancreatitis and its complications.

¹⁷ Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.

GOALS FOR RESEARCH

Objectives:

- Understand genetic factors that predispose to increased risk or severity of acute pancreatitis.
- Understand the role of genetic factors that predispose to chronic injury and/or impaired recovery from acute insults.
- Understand gene-environment interactions in the development of benign and cystic neoplasms, as well as pancreatic cancer arising in the context of chronic pancreatitis.
- Understand the genetic factors that predispose to sensitization and pain in the setting of pancreatic injury.
- Develop novel models of pancreatic disease derived from targeting of specific genes.
- Optimize nutritional strategies for the treatment of acute pancreatitis and its complications.
- Understand the effect of endoscopic approaches (e.g., stents, stone removal, and stricture formation), surgery, and radiologic interventions for the treatment of organized necrosis, pseudocysts, pain, and other complications of acute and chronic pancreatitis.
- Develop novel pharmacologic approaches for the reversal of fibrosis and prevention of islet and parenchymal cell loss, including islet cell and stem cell transplant strategies.
- Understand the role of immunosuppressive therapy for the treatment of autoimmune pancreatitis.

Research Goal 10.4: Develop and validate therapeutic interventions for treatment and/or progression of pancreatitis and its complications.

Much progress has been made in elucidating the signaling mechanisms of inflammation and fibrosis in other disease models, and several cytokines and other molecules have been identified as major players in pathogenesis. Synthetic agents directed against these targets are becoming increasingly available, and their effectiveness in modulating the acute and chronic inflammatory responses in the pancreas needs to be determined. In addition to drugs, endoscopic (e.g., placement of stents) and surgical approaches also hold promise, and their role in the management of acute and chronic pancreatitis needs to be examined rigorously through carefully conducted prospective studies.

Objectives:

- Understand the effects of specific pharmacologic therapies, including anti-cytokine agents for the treatment of acute pancreatitis, as well as the prevention and treatment of necrosis and multi-organ failure.
- Develop novel and more effective pharmacologic and/or endoscopic approaches to prevent ERCP-induced pancreatitis.
- Understand the biologic basis and mechanisms responsible for peripheral sensitization in chronic pancreatitis.
- Understand changes in central sensitization and the underlying mechanisms in patients with painful chronic pancreatitis.
- Understand the biologic basis of narcotic dependence and resistance in patients with chronic pancreatitis.

Research Goal 10.5: Understand the neurobiology of the pancreas with respect to mechanisms of pain and neurogenic inflammation.

Pain is the major symptom that drives patients to seek health care in a variety of pancreatic disorders, including chronic pancreatitis and pancreatic cancer. An understanding of how these disorders affect the sensory nerves conveying pain from the pancreas is, therefore, important for effective therapies to be developed. Further, recent investigations have suggested that communication between the pancreas and its nerves is bi-directional and that neurogenic influences can modify inflammation and perhaps influence the behavior of cancerous cells.

Objectives:

- Understand the biologic basis and mechanisms responsible for peripheral sensitization in chronic pancreatitis.
- Understand changes in central sensitization and the underlying mechanisms in patients with painful chronic pancreatitis.
- Understand the biologic basis of narcotic dependence and resistance in patients with chronic pancreatitis.

GOALS FOR RESEARCH

- Identify novel therapeutic targets for more effective analgesic therapy.
- Understand the mechanisms by which autonomic, spinal, and neurohormonal factors influence the course of acute and chronic pancreatitis and their complications.

Research Goal 10.6: Define the epidemiology and clinical course of acute and chronic pancreatitis, including alcoholic pancreatitis, autoimmune pancreatitis, and cystic fibrosis, through population-based studies in adults and children.

Progress in this area has been hampered by the lack of standardized approaches to diagnosis and classification and the fact that no single center sees enough cases to permit robust and generalizable conclusions. Expanding our knowledge of these issues is critical in order to develop effective estimates of the burden of disease and formulate guidelines for screening, prevention, and treatment. This gap in knowledge is particularly significant for the pediatric population.

Objectives:

- Identify reliable prognostic factors of severity of acute pancreatitis at admission that can be utilized to stratify patients who can be enrolled in studies to evaluate new therapies.
- Understand the co-factors necessary for development of fibrosis in patients with recurrent pancreatitis and the rate of disease progression in chronic pancreatitis.
- Understand the natural history of disease in patients with chronic pancreatitis due to various etiologies, including autoimmune pancreatitis.
- Understand demographic, ethnic, genetic, and environmental factors that elevate the risk of disease development and rate of disease progression.
- Develop and validate reliable measures of pain and quality of life in patients with chronic pancreatitis in adults and children.

Research Goal 10.7: Develop more accurate and useful approaches to the diagnosis of chronic pancreatitis by functional, radiologic, endoscopic, or pathologic/cytologic means.

Innovative strategies are needed for the detection of chronic pancreatitis to enable early diagnosis, predict and monitor disease activity and progression, and distinguish etiopathologic subsets, such as autoimmune or genetic pancreatitis. The pancreas is a relatively small and inaccessible organ. Direct means of evaluating pathologic changes are invasive and carry substantial risk. Most clinical information, therefore, is obtained by indirect means, including biochemical and radiological tests. Research on alternative and/or more accurate tests of form and function will be very important for future clinical progress in pancreatology.

Objectives:

- Develop and validate unequivocal criteria for diagnosis of chronic pancreatitis (histologic and non-histologic) and distinguish etiopathologic subsets, such as autoimmune or genetic pancreatitis.
- Develop novel methods, including minimally invasive biopsy techniques, to help identify patients with early chronic pancreatitis and distinguish etiopathologic subsets.
- Develop and validate novel and less invasive methods to recognize and monitor fibrosis.
- Develop and validate more accurate and convenient tests to assess and monitor pancreatic function.
- Develop and validate reliable noninvasive methods for the diagnosis and monitoring of autoimmune pancreatitis.

Research Goal 10.8: Define the role of pathologic lesions, such as pancreatic intraepithelial neoplasms, and other factors that may correlate with the risk of malignant transformation in chronic pancreatitis and cystic neoplasms and map their morphologic and molecular progression.

GOALS FOR RESEARCH

In a small but important subset of patients, pancreatic cancer develops in the setting of a cystic lesion or chronic pancreatitis. The biologic mechanisms underlying this risk remain unknown, but further knowledge in this area may offer the potential for developing effective methods of surveillance and prevention, including the use of adjuvant/neoadjuvant therapy after partial resection. This may be particularly important in patients with hereditary pancreatitis who are often very young at the onset of their disease and accumulate risk for cancer throughout their life. Other subsets that may benefit include patients with IPMN, in whom large segments of the pancreatic epithelium are vulnerable to cancerous change.

Objectives:

- Understand the epidemiology and natural history of cystic disorders of the pancreas and correlate the findings with the results of imaging and fluid analysis.
- Identify biomarkers in cystic fluid and tissue aspirates for providing unequivocal diagnoses and pathologic distinction.
- Understand the role of invasive and noninvasive methods for surveillance of patients at risk for malignancy.
- Understand the clinico-pathologic correlations involving PanINs, small cystic lesions, and IPMN.
- Understand the genetic and morphologic progression between precursor lesions and pancreatic cancer, particularly in the context of chronic pancreatitis.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Standards for diagnosis: Differences in the diagnosis and care of patients with pancreatic disease impede efforts to compare data across centers or clinical trials. The field would benefit from the development of consensus guidelines for diagnosis of chronic pancreatitis, including histologic and clinical criteria. In addition, validation of reliable tools to measure pain and quality of life in patients with chronic pancreatitis would improve patient care and enhance research efforts.

National resources for pancreas research:

A significant obstacle to research progress on pancreas diseases is that relatively few patients are treated at any single center. Research could be accelerated by pooling data and biosamples and making these resources available to investigators across the U.S.

through a comprehensive national database of acute pancreatitis. Such a database could be used to define mortality and morbidity and to develop reliable prognostic factors of severity at admission, which would enable stratification of patients for enrollment in clinical trials to evaluate new therapies. Similarly, a widely accessible patient registry and a repository of biologic samples for banking tissue, serum, and DNA could increase research on the basic mechanisms of onset and progression of pancreatic diseases. Establishing multicenter consortia for the study of chronic pancreatitis in adults and children would provide opportunities for collaboration among researchers with complementary expertise.

Animal models: Development and validation of animal models of both acute and chronic pancreatitis (alcoholic and non-alcoholic) and its complications would accelerate progress on understanding risk factors for this disease.

Alignment of research and clinical forces: The rapid development of endoscopic and other relatively noninvasive approaches to visualizing the pancreas provides new opportunities for building multidisciplinary research teams that include laboratory

investigators, clinicians, and clinical investigators with different areas of expertise. A concerted effort to align these forces will be important in maximizing the efficiency and productivity of research efforts.