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Acceleration of our understanding of recurrent acute and chronic pancreatitis

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Whitcomb et al. [1] present a new framework for describing chronic pancreatitis in an attempt to shift our definition of the disease from a purely morphologic one to one that incorporates disease mechanisms. This is an important step that is absolutely needed for the field to progress. Clinicians and clinical investigators interested in chronic pancreatitis have long been hamstrung by the lack of consensus in diagnostic criteria. This has led to numerous, and often conflicting, deeply held opinions and approaches to this syndrome. Their paper reviews the historical attempts to define this disease illustrating that our limited understanding of pathogenesis led to descriptions largely limited to morphologic classifications. This approach, inevitably, led to diagnostic criteria that were best suited to identify far-advanced disease, but unable to identify disease at an earlier stage. Early detection is necessary for any effective therapy to be applied to mitigate or reverse the process.

Important to this discussion, there have been significant advances since many previous classifications were devised such as an improved understanding of the effects of genetic mutations [2] and environmental factors such as smoking and obesity [3] in the pathogenesis of chronic pancreatitis. Furthermore, there continues to be a rapidly evolving understanding of the pathogenesis of pancreatic disease. As an example, findings reported in the exocrine pancreas in patients with diabetes [4] show that diabetes can promote fibrosis with minimal effects on inflammation, which has been termed “diabetic exocrine pancreatopathy.” Another example is a recent publication [5] showing that alcohol abuse causes abnormal expression of cystic fibrosis transmembrane conductance regulator (CFTR), which is necessary for pancreatic fluid secretion and when mutated results in chronic pancreatitis morphology. This finding indicates that the deleterious effects of alcohol abuse occur in the ductal epithelium as well as the acinar cell, and both functional components of the exocrine pancreas are in an interplay underlying disease pathogenesis [6].

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A shift to add mechanistic determinants to our definitions of recurrent acute and chronic pancreatitis will also promote the identification and addition of key cellular systems and immune systems that are altered in these diseases. The pancreas is unique with its highly developed protein synthesizing and transport systems. Animal models of pancreatitis demonstrate that disturbances in regulation of calcium signals [7]; protein processing for export in the endoplasmic reticulum and endo-lysosomal system [8,9]; and mitochondrial function [10,11] lead to pancreatitis responses. This is facilitated by critical immune responses in these models, responses that are relevant to human disease [12]. Although these examples of cellular and immune system alterations in experimental models are useful, what is lacking is information about how they are differentially affected by diverse stimuli or combinations of stimuli. Importantly, we lack biomarkers of these pathobiologic responses in humans. This lack of information is a hindrance to development of therapeutics for recurrent acute and chronic pancreatitis.

In the paper by Whitcomb et al. [1], a prolonged process was required to reach the eventual proposed definition. The definition provides, in our opinion, a valuable starting point for the entire pancreas community to build on. The definition connects many essential concepts about chronic pancreatitis, and importantly recognizes the need for additional attention to the early stages of disease. This focus is needed for us to achieve what our patients need, prompt and accurate diagnosis, comprehensive assessment of risk factors and etiologies, and effective intervention to improve quality (and quantity) of life.

In one response to these knowledge gaps, the National Institutes of Health in the United States has initiated The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). This consortium involves a group of 10 investigative sites and one coordinating center in the United States charged with undertaking a comprehensive clinical, epidemiological, and biological characterization of patients with recurrent acute and chronic pancreatitis to gain insight into the pathophysiology of these diseases and potential complications including chronic pain, exocrine pancreatic insufficiency, type 3c diabetes mellitus, and pancreatic cancer.

A key objective of this initiative is to further delineate the mechanisms of this disease, which will inform and permit subsequent improvements to the definition of chronic pancreatitis.

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