

The pathogenesis of chronic pancreatitis

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Summary

To date, there is no consensus on the evolution of chronic pancreatitis. Comfort's initial proposal of acute pancreatitis progressing to chronic pancreatitis was discarded by protagonists of the 'separate' theory. Sarles thus stresses the *de novo* evolution of chronic pancreatitis - acinar protein hypersecretion associated with an imbalance of pancreatic stone promoting and inhibiting factors. However, the 'necrosis-fibrosis sequence' hypothesis of Kloppel and Mallet resurrects the probability of acute pancreatitis leading to chronic pancreatitis. Dimagno offers a unifying concept that the degree of acinar injury determines the natural history of pancreatitis. Uninhibited release of toxic free radicals could be a common end point for various aetiologies resulting in acute or chronic pancreatitis. The pathogenesis of chronic calcifying pancreatitis of the tropics is possibly no different from alcoholic chronic pancreatitis. Neurocrine and paracrine mechanisms have been offered to explain pain out of proportion to radiological and histological pancreatic abnormalities in minimal change chronic pancreatitis.

Keywords: chronic pancreatitis, pathogenesis

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A key controversy in the classification of pancreatitis is whether acute and chronic pancreatitis are separate entities or are two ends of a continuous spectrum of disease. Fifty years ago, Comfort *et al*,¹ hypothesised that recurrent attacks of acute pancreatitis progressed to chronic pancreatitis. This concept was discarded at the first Marseilles meeting (1963) on the classification of pancreatitis.² The consensus that emerged there was that acute and chronic pancreatitis were distinct pathogenetic entities. The 'separate' hypothesis was re-emphasised by the revised Marseilles-Rome classification of 1988.³ More recently, Sarles⁴ has reclassified chronic pancreatitis to emphasise this 'separatism' (table).

Pathogenesis of chronic lithogenic/calcifying pancreatitis (CCP)

SARLES' MODEL

Sarles has persistently emphasised the *de novo* evolution of chronic pancreatitis as distinct from the pathogenesis of acute pancreatitis.^{4,5} Morphometric ultrastructural studies of exocrine pancreas in patients with CCP have provided evidence of acinar protein hypersecretion at the earliest stage (figure 1A), viz, larger nucleus, nucleolus, endoplasmic reticulum and increased number of condensing vacuoles.⁶ This results in hypersecretion of trypsinogen. There is an associated increased ratio of lysosomal hydrolases (cathepsin B) to digestive hydrolases (trypsinogen). This is accompanied by co-localisation of lysosomes and zymogens resulting in intracellular activation of trypsinogen with precipitation of protein (crinophagy).^{7,8} Increased secretion of glucosamino-glycans, neutral and acidic glycoproteins, results in a hyperviscid pancreatic juice.

Lithostathine/pancreatic stone protein (PSP) plays a dominant role in Sarles' hypothesis.⁹ These peptides are hydrolysed by trypsin and cathepsin into Lithostathine H1 and H2. Lithostathine H1 inhibits stone formation, whereas Lithostathine H2/PSP-S1, a 133-amino acid non-glycosylated, insoluble peptide polymerises to form fibrils which form the basic matrix of the protein plug. A similar fibrillar protein was described previously by Gross *et al*¹⁰ as the pancreatic thread protein. In CCP, the messenger RNA for PSP-S2-5 biosynthesis is decreased.¹¹ The zymogen granules and pancreatic juice contain markedly low levels of PSP-S2-5.¹² This translates into an aggressive formation of protein

Table Classification of pancreatitis based on Sarles' 'separate' hypothesis

Pathogenetic class	Sub-classification	Pathology
Acute pancreatitis	Mild pancreatitis	Fat necrosis
	Severe (necrotising) pancreatitis	Coagulation necrosis, haemorrhagic necrosis, with complete recovery if patient survives
Chronic pancreatitis	Lithogenic pancreatitis.	Subtypes based on physico-chemical difference in calculi
	Subtypes:	
	nutritional	
	hereditary	
	hypercalcaemic associated with transparent stones	
associated with pure calcium stones		
Obstructive pancreatitis	Obstruction of MPD precedes pancreatitis	
Inflammatory pancreatitis	Mononuclear cell infiltration with acinar necrosis	
Pancreatic fibrosis	Diffuse perilobular fibrosis	

MPD: Main pancreatic duct.

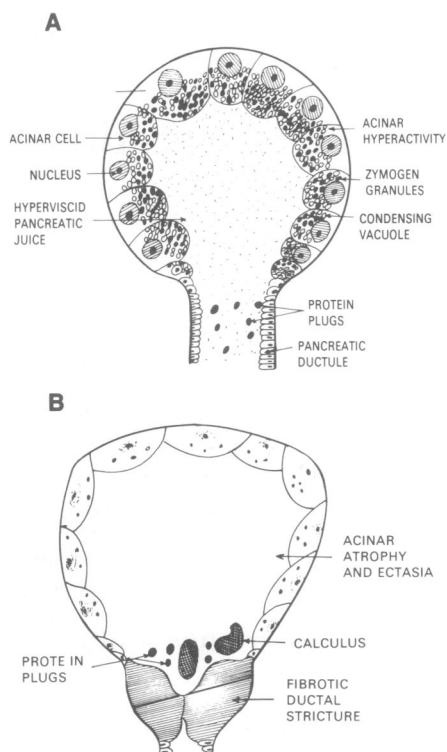


Figure 1 Sarles' model (A) Early chronic pancreatitis—stage of acinar hyperactivity and hyperviscid pancreatic juice with imbalance of pancreatic stone promoters and inhibitors resulting in protein plug formation. (B) Advanced chronic pancreatitis—acinar atrophy, ductal strictures and ectasia with intraductal stones

Pathogenesis of chronic calcifying pancreatitis

- decreased lithostathines production
- frequent attacks of acute pancreatitis
- acinar cell disease
- oxidative stress

Lithostathines

- PSP-S2-5 glycosylated isomers
- MW 16 000–19 000 daltons
- secreted into pancreatic juice
- inhibits protein plug formation and aggregation of calcium carbonate crystals to form stones

plugs and calculi in a favourable milieu of pancreatic juice that is thick, viscid, protein-rich and supersaturated with calcium carbonate. Calcium hypersecretion is originally triggered by neural (cholinergic) or hormonal stimuli. Later the basal lamina of the pancreatic ducts vanishes in contact with protein plugs¹³ which results in transudation of serum protein and calcium¹⁴ into the pancreatic juice. Decreased levels of other nucleation inhibitory factors, such as local trypsin inhibitor and citrate, in pancreatic juice further enhance formation of pancreatic plugs and stones. The ductal strictures and stones finally result in ductal ectasia and acinar atrophy in advanced CCP (figure 1B).

NECROSIS-FIBROSIS SEQUENCE HYPOTHESIS

Kloppel and Maillet^{15,16} have challenged Sarles' concept by resurrecting the theory proposed initially by Comfort *et al*¹ that recurrent attacks of acute pancreatitis lead to chronic pancreatitis. After analysing surgical and autopsy specimens of patients with alcoholic pancreatitis, they hypothesised that peri-acinar and periductal fat necrosis induces periductal fibrosis, which partially obstructs the interlobular ducts causing stasis within ductules, which leads to protein plug and stone formation (figure 2A,B). Subsequently, total obstruction of ducts by calculi induces acinar cell necrosis inflammation and fibrosis (figure 2C). This theory is supported by another study of patients with acute necrotising pancreatitis and chronic pancreatitis showing similar microangiopathic changes.¹⁷ Vascular damage in acute pancreatitis causes cellular anoxia, chronic inflammation, and subsequent fibrosis which are the hallmarks of chronic pancreatitis.

In a recent study, Ammann and Muellhaupt¹⁸ examined this necrosis–fibrosis hypothesis in patients with alcoholic pancreatitis. They found that the yearly incidence of acute attacks of pancreatitis was significantly higher in patients with calcific and noncalcific chronic pancreatitis as compared to patients with nonprogressive chronic pancreatitis. Furthermore, the progression rate to chronic pancreatitis was correlated with severity of acute pancreatitis episodes (associated with pseudocysts in > 55%). Pseudocysts were found to be present more often in the head region (58–71%) in those with progressive chronic pancreatitis as compared to those with non-progressive chronic pancreatitis. These results were compatible with the necrosis–fibrosis hypothesis. The concept of superimposition of acute attacks of pancreatitis over pre-existing chronic pancreatitis could be refuted on the basis of results of an autopsy study of patients with fatal acute pancreatitis.¹⁹ In that study, 53% of specimens from patients with acute alcoholic pancreatitis did not show any evidence of chronic pancreatitis on histology.

ACINAR CONCEPT

DiMagno *et al* offer a unifying hypothesis that chronic pancreatitis begins as a disease of acinar cells.²⁰ The degree of injury to the acinar cells determines the pathogenetic mechanisms and the natural history of pancreatitis. Mild injury increases secretion of pancreatic enzymes and GP-2 (which is a zymogen granule membrane protein related to Tamm–Horsfall protein of renal tubular casts)²¹, and decreases secretion of Lithostathine S and produces abnormal forms of Lithostathine (Lithostathine H2). This leads to intraductal precipitation of protein, obstruction of pancreatic ductules and fibrosis. Mild recurrent injury may insidiously progress to chronic pancreatitis without intermittent attacks of acute pancreatitis. In contrast, severe damage to the acinar cells produces acinar cell necrosis and vascular damage may lead to oxidative stress. This results in recurrent acute pancreatitis, later evolving into chronic pancreatitis.

OXIDATIVE STRESS MECHANISM

This oxidative stress may be responsible for acute recurrent as well as chronic pancreatitis. Induction of pancreatic cytochrome P₄₅₀ enzymes (eg, by alcohol) results in release of excess free radicals.²² This theory is supported by the increased serum molar ratio of octa, deca-9,11-dienoic acid to linoleic acid in such patients.²³ Increased turnover of linoleic acid could, however, also be induced by malnutrition and this might be responsible for the alteration in the ratio. Doubts have also been raised against this model by suggestions that free radicals are probably a common end point of pancreatic inflammation rather than the initiating factor.

OBSOLETE MODELS

Multigner's model

Multigner demonstrated that lactoferrin is present in increased concentrations in the pancreatic juice of CCP patients.²⁴ Lactoferrin associates strongly with acidic macromolecules to form complexes favouring protein precipitation. This

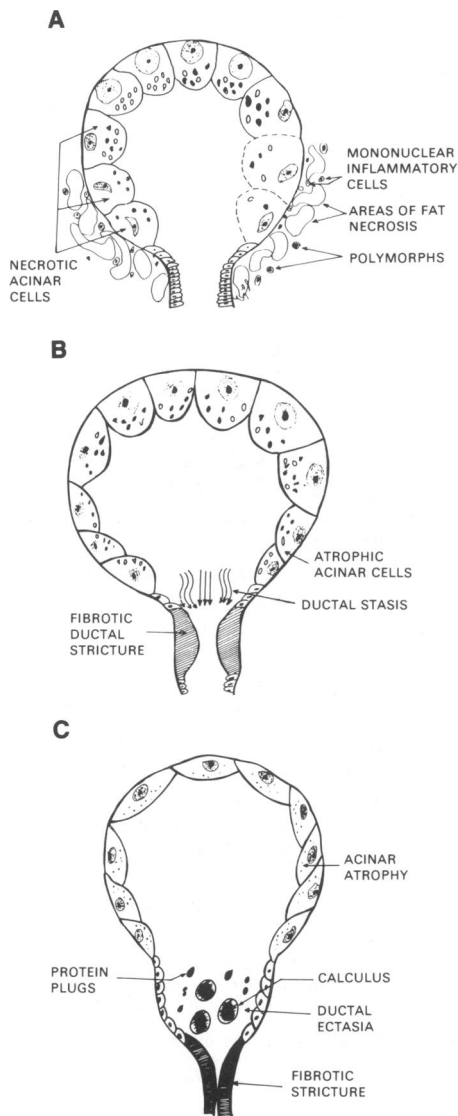


Figure 2 Kloppe & Mailler's model: Acute pancreatitis. (A) Stage of necrosis. (B) Stage of healing and fibrosis. (C) Stage of chronic pancreatitis

Pathogenesis of chronic calcifying pancreatitis of the tropics

- protein calorie malnutrition
- dietary cyanogens
- selenium, zinc, copper deficiency
- viral infections: CMV, mumps

concept has largely been abandoned as a mere epiphenomenon in the natural history of lithogenic pancreatitis.

Direct toxicity of ethanol on the pancreas

Ethanol is metabolised by the pancreas.²⁵ Norohna *et al* thereby conceptualise a direct toxicity of ethanol to explain alcoholic chronic calcifying pancreatitis.²⁶ Alcohol induces lysosomal damage and an increased content of triglycerides in the acinar cells. However, these changes are present in all organs of alcoholics and are reversible. This model failed to explain the formation of plugs and stones.²⁷

We personally favour Sarles' 'separatism' hypothesis—*de novo* evolution of acute and chronic pancreatitis. Hard, consistent morphological data have demonstrated that chronic pancreatitis evolves from an early phase of acinar hyperactivity⁶ with imbalance of pancreatic stone promoters and inhibitors resulting in the formation of protein plugs and intraductal stones.^{11,12} Periductal fibrosis, ductal strictures, ductal ectasia and acinar atrophy appear in advanced chronic pancreatitis. The concept of acute pancreatitis evolving into chronic pancreatitis is based on indirect evidence^{15–17} and remains suspect. However, with no histological evidence of chronic pancreatitis in about 50% of patients with fatal acute alcoholic pancreatitis¹⁹ and the positive results of a recent study testing the necrosis–fibrosis hypothesis,¹⁸ we believe that, at least in a subset of patients, repeated acute insults to the pancreas may result in chronic pancreatitis. Oxidative stress is a common factor in the pathogenesis of acute or chronic pancreatitis which can be turned on by multiple triggers.

Pathogenesis of chronic calcifying pancreatitis of the tropics (CCPT)

The pathogenesis of CCPT is not well understood. The histological changes of extensive acinar destruction, fibrosis, ductal dilatation and comparative preservation of the islets are common to both CCPT and alcoholic pancreatitis. However, inflammatory cell reaction is very rare in CCPT.²⁸ In the earlier stages, however, there are minor distinctive features. Immunoperoxidase staining of pancreatic tissue of CCPT patients for insulin, glucagon, and somatostatin demonstrates cells which are richly stained for these hormones.²⁹ Studies of pancreatic juice in CCPT patients have shown a high calcium content. These stones consisted of 95–98% calcium carbonate in the form of calcite.³⁰ Scanning electron microscopic study of the calculi showed a dense network of intertwining fibres with calcium enmeshed as crystals and in amorphous form on and in between the fibres. Thus, the histological changes and studies on pancreatic juice, calculi and protein plugs indicate a close parallelism between the pathogenesis of alcoholic pancreatitis and CCPT.

Aetiologically the disease is closely associated with malnutrition. CCPT is virtually confined to poor countries, where the diet is poor and *per capita* income low. Protein calorie malnutrition induces a reversible acinar and islet cell atrophy. These patients consume diets low in protein (50 g per day or less) and even lower in fats (less than 30 g per day).^{31,32} Malnutrition of the mother may also play a part in the disease of the child.³³

Dietary cyanogens present in cassava and sorghum consumption have also been implicated.³² This food staple for certain populations, such as in South India, contains cyanogenic glycosides, eg, linamarin and lotaustralin, which release hydrocyanic acid after autolysis or acid hydrolysis, although the method of preparing and cooking the cassava root may also play a role in determining whether or not cyanide is released from the glycoside precursor.³⁴ Finally there is evidence to show that protein calorie malnutrition amplifies the beta-cytotoxic effect of dietary cyanide, because of a lack of the sulphur-containing amino acids that detoxify cyanide to thiocyanate.³⁵ The requirement for both factors in the pathogenesis of beta-cell damage is highlighted by another report that showed that individuals consuming diets of relatively reasonable quantity (> 1900 kcal and 40 g protein) did not have an increased risk of diabetes, despite consuming large amounts of cassava.³⁶ However, the role of kwashiorkor and other factors in the pathogenesis of CCPT has been strongly debated (see box).^{28,32,37,38} Familial clustering (in 28% patients) has also been reported.²⁸

Pathogenesis of chronic obstructive pancreatitis

Obstruction of pancreatic ducts by tumours, papillary stenosis, cysts, scars due to acute pancreatitis, or trauma results in ductal hypertension and ischemia. This results in uniform acinar necroinflammatory lesions with preservation of the ductal epithelium. Calcified protein plugs or pancreatic stones are usually absent.^{4,5}

Pathogenesis of chronic inflammatory pancreatitis

Sarles and Gerolami³⁹ hypothesise an autoimmune mechanism to explain the evolution of this rare disease of elderly patients. Elevated levels of serum gammaglobulin, intrahepatic cholestasis, bilateral sialoadenitis, and nephrotic syndrome in these patients support the concept of immunopathology.

Pathogenesis of minimal change chronic pancreatitis

The separate existence of this form of chronic pancreatitis is controversial. Walsh *et al*⁴⁰ define it by severity of pain out of proportion to the radiological and histological abnormalities of the pancreas. They suggest that neurocrine and paracrine mechanisms may be responsible for this pain since pancreatic drainage and partial pancreatectomy do not relieve it.

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