Leading article

Current views on the pathophysiology of acute biliary pancreatitis

The mechanisms of the pathogenesis of acute biliary pancreatitis include biliopancreatic reflux,1 and obstruction of the pancreatic exocrine secretion either by gall stones,2 biliary sludge,3 or hypertonicity of the ampulla of vater4 (Figure).

Biliopancreatic reflux
There is compelling evidence that biliopancreatic reflux is the main trigger mechanism in biliary pancreatitis. Firstly, surgical sphincteroplasty and endoscopic sphincterotomies improve rather than adversely affect biliary gall stone pancreatitis.5,6 Secondly, patients with one previous episode of gall stone pancreatitis treated conservatively have a recurrence rate of up to 40%, whereas recurrence rates after sphincteroplasty or sphincterotomy are low.7 Furthermore, studies in animals and humans show that ductal obstruction causes reversible oedema fibrosis and acinar atrophy. Thus Opie's postulates, although nearly 100 years old, for the most part probably hold true; namely that biliary obstruction is the initiating event in acute biliary pancreatitis.8

Evidence refuting a major role for duodenopancreatic reflux
While haemorrhagic pancreatic necrosis may not be wholly due to proteolysis, other important mechanisms include oxygen derived free radical action rather than bacterial infection.10 While infected bile is more commonly associated with pancreatitis than sterile bile, this may simply reflect the association of infected bile and gall stone formation. Initially infection was thought likely to account for the endoscopic retrograde cholangiopancreatography (ERCP) induced pancreatitis11 but this is probably due to either local pressure effects12 or possibly osmolarity of contrast media.13 Also, the rich bacterial content in pancreatic necrosis probably reflects superadded infection after the pancreatitis has become established.14 The canine closed duodenal loop model of acute pancreatitis in germ free animals is probably due to duodenopancreatic reflux, which may occur in rare situations such as post-Polya gastrectomy afferent loop pancreatitis.15 Cholangiography at the time of cholecystectomy with some contrast leaking into the duodenum may have some secondary role in the maintenance of the acute episode once initiated.16

Ischaemia as a continuing mechanism
The pancreatic microcirculation is impaired in acute pancreatitis. Capillary stasis may be due to a variety of mechanisms17 including sludging of erythrocytes and haemagglutination, local increases in thromboxanes, generation of oxygen derived free radical species in the microenvironment of the pancreatic ductal-acinar complex, local reduction of endothelial derived relaxation factor (nitrous oxide), and local release of acinar enzymes. There may also be increase in local interstitial pressure as a consequence of obstructed lymph drainage.18 An acinar abnormality may be the initiating factor arising from a combination of ductal obstruction and exocrine hypersecretion19 followed by an increase in intraductal pressure and leakage of enzymes into the pancreatic interstitium17 with zymogen and lysozyme release.18 The increased capillary permeability results in loss of fluid and cells into the interstitium induced by osmolarity shifts either in the duct or extracellular fluid.20 Acute inflammation is followed by vasodilatation and increased blood flow to the gland with severe oedema with a spiral of events leading to further release of enzymes, vasotoxic substances, vascular damage,
and loss of intravascular fluid. Fluid loss into the pancreas and peripancreatic tissues causes a considerable hypo-volaemic response of as much as two to three litres, hypotension, and yet further capillary sludging. Haemorrhagic necrosis occurs with stasis, tissue anoxia, and metabolic acidosis – a self perpetuating series of events. These mechanisms have led to the development of therapeutic approaches including hypertonic saline and dextran, low and high molecular weight dextran, postganglionic sympathetic, peritoneal lavage, and vasopressin.

**Oxygen derived free radicals**

This mechanism is important in pancreatitis of all causes and a direct sequel of biliopancreatic reflux at the onset of acute biliary pancreatitis. There is considerable evidence supporting a central role for oxygen derived free radicals (Figure). Oxygen radicals mediate the depletion of pancreatic sulphhydryl compounds while in both lipid peroxide and oxygen radical scavengers. Serum concentrations of vitamin C, a potent antioxidant, are depleted in acute pancreatitis so that synthetic ascorbic acid derivatives have been used as a free radical scavenger. Finally, changes have been reported in high energy phosphate metabolism and cell morphology in models of acute pancreatitis.

**Proteases, cytokines, and kinins**

Trypsins are involved to some degree while synthetic protease inhibitors E-3123 modulate the response in animal models. Alpha-2-macroglobulin protease complexes are increased in acute pancreatitis while intraduodenal trypsin inhibitor has a protective effect providing supporting evidence for the role of duodenopancreatic reflux. Excessive leucocyte stimulation is seen due to tumour necrosis factor while platelet activating factor antagonist BN 52021 modulates experimental pancreatitis. Trypsinogen may be present in necrotic acinar lobules in excess of inhibitors, at a pH and calcium concentration favouring auto-activation. Trypsin activation could occur from leucocyte derived cathepsin in severe acute inflammatory response with parenchymal necrosis. Either mechanism may further activate elastase, phospholipase, and the kinin system, serving to impair pancreatic perfusion and cause additional necrosis.

**Miscellaneous mechanisms**

Cholecystokinin antagonists and somatostatin reduce hyperamylasaemia but a recent trial showed no protective role for the somatostatin analogue octreotide in the prevention of ERCP induced hyperamylasaemia. Misoprostol, a synthetic prostaglandin E1 analogue is protective in caerulein induced acute pancreatitis in rats.

**Biological variation in the severity of attack**

Innate biological variability between subjects may be responsible in part, for the varied outcome following acute pancreatitis. Recent work has shown a significant decrease in the proportion of T helper cells and increases in interleukin 6 and C reactive protein in severe pancreatitis but not in mild episodes. These findings may be partly explained by translocation of endotoxin from the gastrointestinal tract.

Patients developing fulminant postsurgical sepsis also have evidence of down regulation of T lymphocyte activity, increased monocyte expression of MHC-class II (HLA-DR) antigens, and suppression of the functional activity of neutrophils. They also show selective increases in neutrophil CD11b expression and neutrophil hypochlorous acid production.

If such mechanisms were important in acute pancreatitis then it might be possible to predict those patients likely to develop multiple system failure. Therapeutic possibilities to modify cellular activation profiles include administration of cytokines, for example, granulocyte or colony stimulating factors.

**Conclusions**

Recent advances in basic and clinical research have helped to elucidate the pathophysiology of acute pancreatitis but several challenges remain. The precise sequence of cellular and molecular events that convert localised acute pancreatitis to severe systemic multiple organ failure need to be identified. This, in turn, would permit an accurate prediction of severity. Finally, developments in the new biology should permit effective modification of both the local and systemic effects of acute biliary pancreatitis.

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