References


Pathogenesis of haemorrhagic pancreatic necrosis (HPN)

...— Far from exploding the myth of pancreatic autodigestion as the cause of HPN, Keynes’ progress report (Gut 1988; 29: 1143–25) serves to perpetuate it – merely shifting the point of pancreatic enzyme activation to the duodenum and invoking reflux of the activation product lyssolecithin and/or bacterial toxins (from infected bile) as the mediators of cellular necrosis in gall-stone related disease. The convoluted arguments lack conviction, even in that limited setting, for two main reasons. First, the chronic transpancreatic passage of natural lyssolecithin generating ingredients is innocuous: yet, enforced ductal retention of an artificial brew rapidly causes HPN as does prior manipulation of the ductal permeability barrier. Second, germ free animals do not escape the vicissitudes of the closed duodenal loop. These anomalies (referenced in the review), along with Opie’s classical observations in a human victim, suggest that it is the trapping of bile in the pancreatic duct, whether infected or not, rather than its to and
Correspondence

Recent observations provide a framework within which every facet of acute pancreatitis and HPN can be rationalised without incriminating trypsin, or any substance generated via the activation cascade, as the primary mediator of cellular damage. The initiating agent strikes by ductal, arterial or intracellular route, the problem seems to be triggered by free radical induced disruption of microvascular traffic routes within acinar cells, so that an abnormally large fraction of secretions – zymogens, not activated enzymes – is discharged directly into the interstitium and bloodstream. The self-limiting nature of most clinical attacks may be caused by mobilisation of natural resources to combat oxidant stress, considering the protective effect of antioxidant pretreatment in animal models of oedematous pancreatitis, and the invulnerability of human pancreatic prostates and trypsin inhibitor to an attack by the primary and secondary metabolites of oxygen.

Rinderknecht and I have proposed that the transformation to HPN with multi-system organ failure is initiated by the extracellular secretions from activated leucocytes that are drawn into the gland, especially when debris is present in the pancreatic duct – as in DL-ethionine and bile reflux models, as well as fatal examples of the human disease. Their chemical arsenal, which is usually discharged into the safe confines of a phagocytic vacuole, includes elastase and phospholipase A2, myeloperoxidase which generates the powerful oxidant hypochlorous acid, which in turn inactivates \( \alpha_1 \) protease inhibitor; cachetin; platelet and plasminogen activating factors. These potent chemicals are inadvertently discharged extracellularly when the primary chemoactive stimulant is overwhelming. Free radical oxidation products and bacterial opsonins are powerful chemotactins. Studies of experimental arthritis, however, show that detergents and crystals are especially prone to provoke the response; so, it would be surprising if bile, which is such a powerful stimulant of oxygen free radical production by cells, did not do the same. The concept is in keeping with current thinking regarding the pathogenesis of the shock lung syndrome in other situations. It explains why leucocyte depletion prevented the pulmonary disturbance that otherwise inevitably followed the injection of bile/trypsin into the pancreas and the dramatic improvement after N-acetylcysteine treatment in a patient with sepsis and shock lung from gall stone pancreatitis.

If trypsinogen is indeed an innocent bystander whilst activated leucocytes initiate the carnage of HPN, the case may go down in medicolegal history as the best example of the anathema – 'guilty, until proved otherwise'.

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References


Reply

Sir,—Thank you for allowing me to reply to the letters of Joan Braganza and Michael Blackstone about aspects of my Progress Report (Gut 1988; 29: 1413–23).

The word ‘heretical’ was used in the title as my report was a challenge to the long held accepted truths contained in the publications of Opie 1901–1909. The first section clearly was concerned to show that autodigestion could not be a result of the activation of the pancreatic proteolytic enzymes, a theme with which Dr Braganza appears to agree, and which recently received a backup. I mentioned the possibility of another system, involving the duodeno-pancreatic reflux of lysolecithins as a cause of the necrosis of haemorrhagic pancreatitis, and using an argument which was only convoluted in trying to