Correspondence

Pancreatitis from intestinal reflux – Again?

Sir,—Twenty years after the publication in Gut of McCutcheon’s ‘fresh approach’ to the pathogenesis of acute pancreatitis,1 we now have Keynes’ ‘heretical thoughts’ (Gut, 1988; 29: 1413–23). Both articles are highly polemical essays promoting the intestinal reflux theory, especially for acute pancreatitis from gall stones. Keynes now offers the readership of Gut his intestinal bacteria hypothesis,2 namely that gall stones cause haemorrhagic pancreatitis only when migration of the stone across the ampulla causes Sphincter of Oddi incompetence allowing for duodenopancreatic reflux containing ‘...cytotoxin producing bacteria or toxic bacterial products ...’ which cause acinar cell necrosis and haemorrhage.

Yet clinical experience is at variance with the intestinal reflux theory. First, surgical sphincteroplasty3 and endoscopic sphincterotomy4 though further rendering the Oddi sphincter in effect even more incompetent5 or ablating it altogether improve rather than worsen acute gall stone pancreatitis as would be predicted by the intestinal reflux theory. Moreover, longterm studies of sphincteroplasty for gall stone pancreatitis reveal a low a to absent incidence of recurrence, contrary to the expectation of the intestinal reflux theory. In addition, recurrence of pancreatitis after surgical sphincteroplasty for non gall stone pancreatitis is not known to be more severe than that occurring in the absence of surgery, so a critical role for refluxed bacteria as promoters of haemorrhagic pancreatitis seems highly unlikely, although in some cases, there might be a contribution of resident pancreatic flora to pancreatic sepsis occurring in haemorrhagic pancreatitis; an often lethal combination.6

Keynes correctly argues that lethal haemorrhagic pancreatitis does not occur simply from ductal obstruction which only causes reversible oedema, fibrosis and acinar atrophy in experimental settings,7 as well as in man.8 This, however, does not exclude obstruction as the beginning of the progression to haemorrhagic pancreatitis, only that it is exceptional, occurring in no more than 15% of patients, even of those who die of acute obstructive (gall stone) pancreatitis,10 and not at all in aminals with experimental ductal obstruction.10

A factor likely to be important in the progression to haemorrhagic pancreatitis although not considered by Keynes, is the vascular response to obstruction.11 In animals with an intact pancreatic vasculature, when interstitial (‘oedematous pancreatitis’) is experimentally produced, there is an associated increased perfusion.12,13 When the vasculature is experimentally impaired in the presence of ductal obstruction and oedema, however, haemorrhagic pancreatitis occurs.14 Decreased perfusion is also observed in conjunction with oedema and vascular injury, potentially serving to further promote haemorrhagic pancreatitis.15

The variable pancreatic injury found at surgery and autopsy in acute gall stone pancreatitis is explainable in terms of the vascular response to obstruction and the duration of the obstruction, with haemorrhagic pancreatitis being exceptional, occurring only when pancreatic perfusion is inadequate to maintain oxygenation and nutritive support of acinar cells in the face of oedema.

Fortunately, in gall stone pancreatitis the transient nature of obstruction16 typically occurring from very small calculi17 coupled with an adequate vascular response may allow for what is usually a selflimited episode.17 More prolonged obstruction, however, particularly in elderly patients who are at greatest risk for an inadequate vascular response may be a predisposing factor for an adverse outcome,18 but one which can be reversed with timely intervention to relieve the obstruction.19

Obstruction, therefore, which in exceptional circumstances leads to ischaemic necrosis, rather than reflux of cytotoxin producing bacteria, is a more likely mechanism for the widespread acinar cell necrosis recognised at autopsy in haemorrhagic pancreatitis. It is tempting to speculate that if the ischaemic necrosis were massive enough, trypsinogen might be present in necrotic acinar lobules in excess of inhibitors, at a pH and calcium concentration favouring autoactivation.20 Alternatively, in the presence of the severe acute inflammatory response which occurs with parenchymal necrosis,21 trypsin activation could occur from leucocyte derived cathepsins.22 Either mechanism may further serve to activate elastase,24 phospholipase A,25 and the bradykinin system,26 further serving to impair pancreatic perfusion and cause additional parenchymal necrosis as well as to promote the systemic absorption of activated enzymes which both in animal models,27 and man28 is associated with the multisystem failure27 seen before death from haemorrhagic pancreatitis.

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References


Pathogenesis of haemorrhagic pancreatic necrosis (HPN)

str., — Far from exploring 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 lysolysithin 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 lysolysithin 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 Oppie’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
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