from movement across an incompetent Sphincter of Oddi that predisposes to the catastrophe.

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.¹ Whether the inciting agent strikes by ductal, arterial or intracinar route, the problem seems to be triggered by free radical induced disruption of microtubular 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,² and the invulnerability of human pancreatic proteases and trypsin inhibitor to an attack by the primary and secondary metabolites of oxygen.³

Rinderknecht and I⁴ 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.¹ 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 α_1 protease inhibitor; cachetin; platelet and plasminogen activating factors.^{1,5} These potent chemicals are inadvertently discharged extracellularly when the primary chemotactic 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,⁶ did not do the same. The concept is in keeping with current thinking regarding the pathogenesis of the shock lung syndrome in other situations.^{1,7} It explains why leucocyte depletion prevented the pulmonary disturbance that otherwise inevitably followed the injection of bile/trypsin into the pancreas⁷ and the dramatic improvement after N-acetylcysteine treatment in a patient with sepsis and shock lung from gall stone pancreatitis.⁸

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'.

JOAN M BRAGANZA

Manchester Royal Infirmary,
Oxford Road,
Manchester M13 9WL.

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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.¹ 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

include it as 'proteolytic autodigestion'. Dr Braganza does not like this, and now closely argues for something that does not involve proteolysis in the usual sense of the word. Since 1896, proteolysis has been, of course, the accepted cause of autodigestion.

Dr Braganza has convincingly expanded on my passing references to oxygen derived free radicals as a cause of acute haemorrhagic pancreatitis. Most interestingly from my point of view, in 1983 she related the production of pancreatitis to the duodenopancreatic reflux (so hated by Dr Blackstone) of toxic products generated by free radical oxidation in the liver.² In my report, I concentrated on reflux of duodenal fluid into the pancreatic duct, and, through lack of space, hardly mentioned reflux of bile. I do not, though, fully understand Dr Braganza's sweeping remark that 'it is the trapping of bile in the pancreatic duct, whether infected or not, rather than its to and fro movement across an incompetent Sphincter of Oddi that predisposes' to necrotic pancreatitis. Nor, can I understand her last paragraph, including the use of the word 'anathema' which means 'a solemn ecclesiastical curse or denunciation involving excommunication', or 'an object of abhorrence'!

Dr Blackstone repeats the arguments he used after an editorial last year in the *Lancet*.^{3,4} He is dismissive of what he calls my 'intestinal bacteria theory', and in his first paragraph is economical in the use of what I actually wrote. In his last paragraph, his succumbing to the temptation to speculate on the biochemical effects of ischaemic pancreatic necrosis adds little comment, though some support, to my report. Moreover, in its references to the pancreatic proteases, it neglects, by inference, my arguments against their ability to be destructive and cause autodigestion. And, I did not write that in every patient with haemorrhagic pancreatitis was it caused by reflux of cytotoxin producing bacteria.

The magnificent results being obtained, using computed tomography guided, or open, drainage of infected necrotic tissue in the treatment of haemorrhagic pancreatitis, by E L Bradley's group in Atlanta, Georgia, and H G Beger's group in Ulm, have added to the timeliness of my section on the bacteriology of such pancreatitis. The argument still remains whether the infection is primary or secondary, and, in favour of a primary infection, there is the experimental work, the earliness in the disease in which bacteria have been detected in those infected, and the rarity in those shown to have a sterile necrosis for it subsequently to become infected.^{5,7} It is unsatisfactory to claim, without evidence, that there is a simple diathesis of the 'gut' organisms to infect necrotic pancreas, but how does the infection occur? For both primary and secondary infection, reflux is an obvious answer.

ERCP and endoscopic sphincterotomy are both followed by a definite incidence of pancreatitis,⁸ as is surgical sphincterotomy and other conditions that interfere with the competence of the sphincter of Oddi. It is not clear for how long incompetence of the sphincter remains after endoscopic and surgical interference, or the passage of a gall stone, but, if it persists, other factors must be involved to give pancreatitis. And, I repeat, I did not write that all cases of haemorrhagic pancreatitis result from reflux of bacteria from the duodenum (or of infected bile). I was content to argue that reflux was a cause of both interstitial and haemorrhagic pancreatitis, and might typically follow from a gall stone damaging the competence of the sphincter. I continue to believe, then, that clinical experience is not at variance with any reflux theory, as claimed by Dr Blackstone.

The mere presence of gall stones does not establish the mechanism by which they may cause acute pancreatitis. Dr Blackstone agrees that complete ductal obstruction does not give acute pancreatitis, and, if I read his letter correctly, that obstruction may only be present at the beginning to give an attack of pancreatitis. At present, 'the most widely accepted view is that acute pancreatitis is caused by hypertension in the pancreatic duct.'⁹ In my report, I did not consider the vexed question of pressures in the common bile duct and pancreatic duct, but, for reflux of duodenal fluid, or of bile, into the pancreatic duct, there must be pressure changes from normal. I used a pathophysiological approach, and mentioned what happens on increasing the pancreatic duct pressure, that it gives the changes of interstitial pancreatitis. I thought I implied, without spelling it out, that on reflux there could be a relative rise in ductal pressure giving the same effect as temporary ductal obstruction. At this, it seems possible that Dr Blackstone's predilection for obstruction rather than reflux might be overcome.

I have read with interest Dr Blackstone's experimental evidence for ischaemic pancreatic necrosis after ductal obstruction, and will make two comments. It seems from his description that its acceptance, at least partially, depends on a pathological assessment that he has not provided – as in my third section – and that having grasped this 'nettle' of a theory he has gone overboard in his enthusiasm for obstruction rather than reflux. Ischaemic pancreatic necrosis may very well explain some examples of haemorrhagic pancreatitis, but, as with my 'intestinal bacteria hypothesis', cannot explain them all.

MILO KEYNES

Department of Anatomy,
Downing Street,
Cambridge CB2 3DY.

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Bowel rest and nutritional support in the management of Crohn's disease

SIR,—We read with interest the paper by Dr Greenberg and colleagues (*Gut* 1988; **29**: 1309–15) who report a trial of bowel rest and nutritional support in the management of Crohn's disease. Remission rates were similar in groups of patients treated by bowel rest and total parenteral nutrition (TPN), oral diet (OD) with supplemental parenteral nutrition and enteral diet. Consequently it was concluded that any benefit was derived from nutritional support and not bowel rest. Unfortunately both the TPN and OD groups received part of their non-protein energy as intralipid. Intralipid has an immunomodulatory effect, impairing monocyte and phagocyte function.¹ The possibility that such an influence may mask any impact of oral feeding on disease activity does not appear to have been considered either in this paper or in the accompanying editorial (*Gut* 1988; **29**: 1304–8). Contrary to the views expressed in this editorial we believe the case against bowel rest remains unproven. Furthermore our own group has found very high levels of antibody to *Saccharomyces cerevisiae* (baker's yeast) in patients with Crohn's disease, but not in patients suffering from ulcerative colitis.² The presence of mannans in cell wall structures in both yeast and atypical mycobacteria³ raises the possibility that Crohn's disease develops when predisposed individuals become sensitised to such dietary components after infection with atypical mycobacteria. In the light of our findings, it would

seem important that the effect of oral intake is not obscured by other manipulations. Further work is required to determine the effect, if any, of dietary components on disease activity.

C R PENNINGTON, H MCKENZIE, J MAIN, AND D PARRATT
Departments of Medicine and Microbiology,
Ninewells Hospital and Medical School,
Dundee

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Reply

SIR,—We thank Dr Pennington and colleagues for their interest in our study. Remission rates were comparable in groups of patients treated by a defined formula diet (polymeric feeding without Intralipid) and by TPN (nil *per os* with Intralipid). Thus, it is unlikely that Intralipid masked an effect by feeding on disease activity. Although specific and direct immunomodular reactions by intravenous fat preparation on the activity of Crohn's disease were not examined in our study, proof of such a phenomenon would only add to the contention that provision of nutritional support, rather than bowel rest was the major factor contributing to remission in our patients. It is also noteworthy that effects reported by Fischer *et al* (quoted in your letter) are achieved at lipid concentrations that are three-fold greater than occurs in our patients receiving TPN and 15 fold greater than in patients receiving PPN. Moreover, subsequent studies by others^{1–3} have shown no immunosuppressive effect after lipid. The yeast hypothesis is intriguing; we look forward to any findings that provide insight into the pathogenesis of Crohn's disease.

G R GREENBERG AND K N JEEJEBHOY

Division of Gastroenterology,
Toronto General Hospital,
University of Toronto, Toronto,
Ontario, Canada M5C 2C4

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