LETTERS TO THE EDITOR

Hepatic aberrations in patients with chronic pancreatitis

EDITOR,—The article by Jalleh *et al*¹ describes a high frequency of portal tract changes in operative liver biopsy specimens from 52 patients undergoing surgery for chronic pancreatitis (alcoholic aetiology 77%). A study by our group in 1986² recorded the same phenomenon in 38 consecutive non-jaundiced patients who had a biopsy (usually percutaneous) between 10 days and six months after an attack of pancreatitis (alcoholic 8, miscellaneous 9, idiopathic 21) which was classified as acute in eight cases and acute on chronic in 30 cases. The portal tracts were abnormal in 28 cases (74%); the changes included diffuse lymphocytic infiltration, focal bile duct proliferation, focal ductopenia, and features suggesting primary sclerosing cholangitis or primary biliary cirrhosis. We also noted subtle changes, including siderosis, in hepatocytes occupying 10–100% of parenchyma in 23 cases (60%). The abnormal cells were sometimes large and water clear and sometimes had the typical appearance of ground glass hepatocytes.

We suggested: (a) that the aberrations in hepatocytes represented hepatic enzyme induction from chronic exposure to xenobiotics with superimposed damage from toxic metabolites; (b) that the portal tract disturbances were initiated by the entry of excessive amounts of lipid oxidation and other toxic metabolites in bile. Support for enzyme induction came from parallel studies of drug metabolism³ and hepatic morphometry.⁴ The idea of toxic metabolite related damage was reinforced by morphological evidence of excessive deposition of lipofuscin and microvesicular steatosis, or both, and dilated endoplasmic reticulum on electron microscopy; together with biochemical evidence from the amounts and types of lipid oxidation markers in secretin stimulated bile.^{5,6} With regard to the possible connection between increased outputs of reactive intermediates in bile and initiation of portal tract inflammation, there is evidence that free radical activity causes alterations in the structure of gamma-globulins.⁷ The longstanding preoccupation of pancreatologists with the idea that abnormal bile may reflux into the pancreas and initiate damage therein, led us initially to take the argument further in that direction. Only when surgical diversion of this abnormal bile failed to stop the course of pancreatitis in three patients⁸ did it become clear that pancreatic and liver damage proceeded independently.

If reflux, however, was also to occur—as was shown unequivocally in one of those patients⁷—it would be expected to compound damage in the head of the gland. Of further interest was the finding that pancreatic acinar cells from that patient (who had had a Whipple operation) showed microvesiculation very similar to that in his hepatocytes. Immunocytochemistry of tissue fragments from subsequent patients, and organ donor controls, have now proved the constancy of hepatic and pancreatic cytochrome P450 induction in patients with chronic pancreatitis,⁹ while clinical trials, both anecdotal¹⁰ and placebo controlled,^{10,11} have

shown the value of antioxidant supplementation in controlling symptoms. The concept that oxidative stress, through induced cytochromes P-450 in pancreatic cells, is central to the pathogenesis of chronic pancreatitis rationalises the recent report from Bourliere *et al* in the same issue of *Gut*.¹² The authors concluded that cigarette smoke and alcohol are distinct risk factors for pancreatic damage in chronic pancreatitis, but not for liver injury. Whereas ingested xenobiotics such as alcohol would preferentially reach the liver, inhaled xenobiotics would strike the pancreas directly. The concept predicts that diets enriched in corn oil, a potent inducer of cytochrome P-450L, should facilitate the development of an experimental model of chronic pancreatitis.^{13,14}

Free radicals are not the only tissue damaging principle: others include proteases and phospholipases from inflammatory cells, and cytolytic properties of a complement cascade. The corollary is that the outcome of oxidative stress is different within different organs—depending upon the inherent antioxidant capacity, as well as populations of resident macrophages and immune systems to amplify and perpetuate injury. The liver with its generous quota of each of these systems is better equipped than the pancreas to resist wholesale cellular destruction from oxidative stress but, paradoxically, may display the kind of subtle changes that have now been documented in portal tracts and macrophages. We find it difficult to accept the alternate explanation by Jalleh *et al* that these changes are secondary to inflammation of the pancreas, for the reasons discussed above.

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Reply

EDITOR,—Thank you for the opportunity to respond to the above correspondence. We find no conflict in the information presented in the two studies. Rather, comparison with the study recently reported from our laboratory¹ and that previously reported by Drs Haboubi, Ali, and Braganza² reveals many important similarities.

Portal lymphocytosis. It is of interest that, in the paper by Haboubi *et al*, they describe infiltration of portal tracts as the main abnormality in 74% of patients. This high incidence of portal lymphocytosis is similar to the incidence of 92% found by us (particularly since these two studies were not matched). The importance of our study is not only the presence of chronic inflammatory cells but also the finding that they are almost exclusively T lymphocytes and that they occur in excess numbers in an organ that shows no evidence of cell mediated cytotoxic damage.

Hepatocyte morphology. The report of Haboubi *et al* included 30 cases of chronic pancreatitis (20 men, 10 women) with a mean age identical to that of our study (41 years). In their study, liver biopsy was performed at variable intervals after an acute attack of pancreatitis whereas, in our series, liver biopsy was performed intra-operatively when all patients had been free from alcohol for several weeks and their disease was clinically quiescent. It is hardly surprising, therefore, that mild acute morphological changes to hepatocytes, predominantly steatosis and intracellular oedema, should be more frequent in their study than in ours (60% v 42%).

Toxic metabolite theory. The hypotheses of Dr Braganza and her colleagues concerning the possible effects of toxic metabolites on hepatocellular function in chronic pancreatitis are well known.³ The results reported in their series published in 1986² do not conflict with the data recently published from this laboratory. Unfortunately, their paper does not fulfil Koch's postulates by demonstrating a causal relationship between morphological changes in hepatocytes and coincidental abnormalities in drug metabolism. No paired study was performed to control the effect of alcohol on the liver in the absence of chronic pancreatitis and hence to assess the effect of alcohol on the data.

Aetiopathogenesis of chronic pancreatitis. We certainly agree with the statement from Dr Braganza and coworkers that the pathogenesis of chronic pancreatitis is unclear⁴ and that abnormal bile reflux into the pancreatic duct is unlikely to initiate the disease. Our paper has not discussed the pathogenesis of hepatic dysfunction in chronic pancreatitis since, even in those patients with a history of excessive alcohol consumption, the true aetiology of their disease is presently uncertain.

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Helicobacter pylori infection rates in relation to age and social class in a population of Welsh men

EDITOR,—We previously reported results from a study looking at the prevalence of *Helicobacter pylori* IgG antibodies in a population of 749 randomly selected men, aged 30-75 years, from Caerphilly, South Wales.¹ Evidence has recently been presented to suggest that acquisition of *H pylori* infection is related to childhood living conditions.^{2,3} In our study, information was available on current and past household size for 563 men and we have now analysed this in relationship to antibody prevalence. There was a strong linear trend between antibody prevalence and the number of the subjects' siblings (see Table). This is consistent with the reported relationships between antibody prevalence and childhood domestic crowding² and sharing a bed as a child.³ We found no relationship between antibody prevalence and the number of children currently sharing the same household as the subject (unlike Mendall *et al*).² nor was there a relationship with the number of adults currently sharing the household (consistent with Mendall *et al*).

The associations observed in the two studies^{2,3} and our own suggest that early social environment may be of particular significance in relation to *H pylori* transmission. If *H pylori* infection occurs primarily as a result of childhood contact, then the positive relationship between *H pylori* prevalence and age, which has been repeatedly observed,⁴ may partly reflect a decrease in childhood acquisition rates over time—that is, a cohort effect.⁵ Such an effect is illustrated in the data from Caerphilly (See Figure) which shows the prevalence of *H pylori* by decade of birth and social class (this was previously presented by age and social class). The prevalence was extremely high in those born at the beginning of the century, decreasing during successive birth cohorts, with the decline being most rapid for those in upper social class groups. We suggest that if early childhood is a particularly critical period for

Table Total number of men and number (%) positive for *Helicobacter pylori* IgG antibodies in Caerphilly by number of siblings and by number of children (aged <17 years) and number of adults (≥17 years) in current household

		Total No of men	No (%) of men positive
Number of siblings	0-1	150	59 (39.3)
	2-3	193	101 (52.3)
	>3	220	138 (62.7)
			χ^2 (trend) ¹ =6.69 p<0.01
Number of children in current household	0-1	367	210 (57.2)
	2-3	164	73 (44.5)
	>3	32	15 (46.9)
			χ^2 (trend) ¹ =0.05 NS
Number of adults in current household	1-2	361	175 (48.5)
	3	117	70 (59.8)
	4	85	53 (62.4)
			χ^2 (trend) ¹ =0.40 NS

¹ Adjusted for age (30-34, 35-44, 45-54, 55-64, 65-69) and social class (I and II, III, IV and V).

acquisition of *H pylori* infection then improvements in living conditions will have resulted in reduced acquisition rates in the United Kingdom during the century as seen in the Figure. Such a pattern of declining infection would be consistent with decreases in suspected *H pylori* associated diseases, notably duodenal ulcer⁶ and gastric cancer⁷ observed in the United Kingdom in recent decades.

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Prevalence of *H pylori* IgG antibodies in men from Caerphilly by year of birth and by social class. (Based on sampling in 1979, ie men born in 1910-19, 1920-29... were 60-69, 50-59... etc.)

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Sulphasalazine in ulcerative colitis

EDITOR,—A recently completed review is strongly supportive of the opinion expressed in the leading article,¹ that the mechanism of therapeutic action of sulphasalazine in inflammatory bowel diseases is different from that of various newer sulphonylurea free 5-aminosalicylic acid (5ASA) preparations. The review² which studies anti-inflammatory drug treatment of radiation induced damage has shown that both acute and chronic enterocolitis responded favourably to sulphasalazine in all series published to date³⁻⁷. In direct contrast, 5ASA administered orally (Baughan CA, *et al*, unpublished data), in enemas^{8,9} or suppositories¹⁰ was, at best, ineffective and tended to cause symptomatic worsening of radiation enterocolitis/proctitis.

The inflammatory reactions of the gut to ionising radiations have not been well characterised. They differ from those of the idiopathic inflammatory bowel diseases because in radiation enteritis both subjective and objective improvement has been found in response to non-steroidal anti-inflammatory drugs including aspirin.⁴ This suggests that the endogenous cyclooxygenase products are deleterious, unlike in idiopathic inflammatory bowel diseases.¹ The difference, however, in therapeutic effectiveness between sulphasalazine and 5ASA shown for a common complication of radiotherapy to the abdomen or pelvis illustrates well a basic divergence in the respective modes of drug action.

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