LETTERS TO THE EDITOR

"Non-alcoholic duct destructive chronic pancreatitis" or "primary chronic pancreatitis"?

EDITOR,—We read with great interest the article by Ectors *et al* (*Gut* 1997;41:263-8) in which the authors describe a particular form of chronic pancreatitis in patients without chronic alcohol intake. The authors suggest the term "non-alcoholic duct destructive chronic pancreatitis" for this type of pancreatic disease in order to stress: (1) the absence of any history of alcohol abuse; (2) the target of the chronic immunological reaction; and (3) the destructive nature of the process. Characteristically some of these cases were associated with an autoimmune disease, such as primary sclerosing cholangitis, ulcerative colitis, Crohn's disease, or Sjögren's syndrome. The authors conclude that the inflammatory changes in the pancreatic ducts observed in this particular form of chronic pancreatitis are suggestive of an autoimmune process.

A few years ago our group postulated a new hypothesis for the pathogenesis of a particular form of chronic pancreatitis, which we defined as "primary chronic pancreatitis".¹ We suggested that the key step in the pathogenesis of this type of chronic pancreatitis may be an immune reaction against a pancreatic target antigen in the epithelium of the pancreatic ducts, with secondary inflammatory infiltration (mainly by T lymphocytes) around the main and/or secondary pancreatic ducts followed by an obliterating periductal fibrosis. This immune mediated hypothesis was based on clinical associations between chronic pancreatitis and autoimmune diseases,² in view of the histological and radiological analogies between chronic pancreatitis and primary sclerosing cholangitis.

Other studies have since confirmed our hypothesis. Kino-Ohsaki and colleagues³ demonstrated the presence in patients with chronic pancreatitis of antibodies to carbonic anhydrase I and II, an enzyme present in the epithelium of the pancreatic and biliary ducts and the gastrointestinal tract.⁴ Later, Puig-Divi and coworkers⁵ reproduced morphological pancreatic changes mimicking the features of human chronic pancreatitis in a new experimental model obtained without ligation of the main pancreatic duct and involving an immune mechanism. In particular, in this animal model of chronic pancreatitis, the disease was induced in rats by instillation of trinitrobenzene sulphonic acid (TNBS) into the pancreatic ducts. This substance is capable of coupling membrane proteins, of modifying the structure of the epithelial surface of the pancreatic ducts and, therefore, of inducing an immune reaction to a new, previously unrecognised antigen.⁶ Interestingly, intracholedochal and colonic administration of TNBS in rats may induce chronic cholangitis of the small ducts⁷ and ulcerative colitis,^{8,9} respectively. More recently, Hunger and colleagues¹⁰ have demonstrated a preferential activation of cell mediated cytotoxicity in the pancreas of patients with alcoholic chronic pancreatitis and postulate that an immune reaction is involved in

tissue destruction in this condition. By and large, these studies seem to show that chronic pancreatitis may be induced by an immune mediated mechanism and that this mechanism might explain the clinical associations between chronic pancreatitis and sclerosing diseases of the biliary tract (primary sclerosing cholangitis and primary biliary cirrhosis) or chronic inflammatory diseases of the gastrointestinal tract.

In the study by Ectors *et al* the pancreas in non-alcoholic chronic pancreatitis was characterised by dense lymphocyte infiltrates (mainly T lymphocytes) around the interlobular ducts with a patchy distribution. These changes, which are quite different from those in alcoholic chronic pancreatitis, lead to a periductal obliterating fibrosis and, later, to replacement of acinar parenchyma with fibrous tissue upstream of the ductal stenosis. In our opinion, the "non-alcoholic destructive chronic pancreatitis" suggested by Ectors *et al* probably represents a severe form of "primary chronic pancreatitis". Their study, in fact, presents a selection bias: the authors examined pancreatic specimens obtained from patients treated by resection because of such severe inflammation of the pancreas involving the biliary tract, that carcinoma of the head of the pancreas was clinically suspected. However, the clinical expression of "primary chronic pancreatitis" is probably more heterogeneous and we believe that many patients with the classic symptoms of chronic pancreatitis and a mild-to-moderate form of "primary chronic pancreatitis" may be misdiagnosed in the absence of histological findings. Moreover, we wish to stress that it is incorrect to divide chronic pancreatitis into alcoholic and non-alcoholic forms and to postulate that an immune mediated mechanism is present only in idiopathic chronic pancreatitis. Alcohol abuse, like cigarette smoking, may produce structural alterations in the membranes of the pancreatic duct epithelium, directly or indirectly via the production of acetaldehyde, and trigger an immunological response in genetically predisposed subjects. In our clinical series, calcifications were present in four (57%) of seven patients with chronic pancreatitis and ulcerative colitis,¹¹ and in seven (78%) of nine patients with chronic pancreatitis and chronic sialadenitis.¹² In all of these patients with chronic pancreatitis, autoimmune diseases and pancreatic calcifications we documented chronic alcohol intake and/or cigarette smoking. The absence of protein plugs and intraductal calcifications shown by Ectors *et al* in non-alcoholic chronic pancreatitis probably reflects the incorrect inclusion criteria.

In clinical practice, we therefore prefer to divide patients with chronic pancreatitis into those with "primary chronic pancreatitis" (immune mediated disease) and those with "secondary chronic pancreatitis" (obstructive disease). If this simple classification is accepted, the future clinical challenge will be to identify reliable criteria for diagnosing primary or secondary chronic pancreatitis.

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Guidelines for treatment of acute pancreatitis

EDITOR,—The British Society of Gastroenterology should be congratulated for commissioning the guidelines on the management of acute pancreatitis (*Gut* 1998;42(suppl 2):S1-13). However, in this document the clinically relevant issue of drug treatment of acute pancreatitis has not been reviewed in depth. Although we agree that current treatment of severe necrotising pancreatitis is unsatisfactory, we do not share the opinion that beyond resuscitation and support there is no agreed specific treatment. We would like remind members of the working party and the experts who have reviewed the document that in two previous meta-analyses, both somatostatin and gabexate mesilate seemed to reduce, respectively, mortality and complications in these patients.^{1,2} Despite this evidence, the use of these drugs has not been recommended or even discussed; based on a single randomised controlled trial in which somatostatin was given for only two days in very small doses, all therapeutic options have been dismissed by the working party as of unproved value.

The authors of the guidelines recognise that as new evidence comes to light, the document will need to be reviewed continuously. A recent meta-analysis has been published in which a total of 25 controlled clinical trials exploring the usefulness of somatostatin (11 studies), octreotide (eight studies), and gabexate mesilate (six studies) in patients with acute pancreatitis has been evaluated. The analysis has shown that the first two agents reduce mortality without affecting complications, and that gabexate mesilate reduces complications but not mortality.³ Given the lack of interaction between this latter agent and somatostatin and octreotide, a future trial exploring the effi-

cacy of combining these drugs might be of great help. Presently, the data in the three meta-analyses constitutes a sound, objective basis on which to tackle therapeutic decisions.

The statement endorsed by the working party seems to reflect the common belief shared by leading authorities in this field that these agents are ineffective in the treatment of acute pancreatitis. This may be because the drugs are believed to act through their antisecretory or protease inhibitory activity. However, other relevant properties of somatostatin and octreotide, namely the haemodynamic effects on reducing splanchnic blood flow, the stimulation of the hepatic reticuloendothelial system, and the modulation of the cytokine cascade, are usually forgotten. It has been hypothesised that the efficacy of somatostatin and octreotide in acute pancreatitis might be better explained by all these properties rather than its capability of inhibiting pancreatic secretion.³

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Colonoscopic surveillance in ulcerative colitis

EDITOR,—The study by Karlen *et al* (*Gut* 1998;42:711-14) makes the reader wonder how the authors could draw a conclusion that is suggestive of a positive outcome when the data analysis clearly shows no statistical significance.

It is well established that mortality from colorectal carcinoma is an important factor in patients with ulcerative colitis. However whether surveillance programmes have any effect on mortality is still matter of debate.¹⁻⁴ Furthermore for the practical and ethical considerations mentioned by Karlen *et al* in their introduction, it is unlikely we would ever have a randomised controlled trial to look at the value of colonoscopic surveillance in this respect. It is likely that we will come to rely on studies such as Karlen *et al*'s.

It is for this reason that we should scrutinise the methods and results of such studies closely so that we can draw appropriate conclusions. Karlen *et al* studied 4664 subjects with a definite diagnosis of ulcerative colitis from an approximate background population of 3 million people in two regions of Sweden. The patient group was identified as "all patients in the study population that had died from colorectal cancer after 1975", which amounted to 40 cases. The aim of the control population was to have three controls for each patient matched individually by age at diagnosis (± 5 years), duration of disease,

extent of disease at diagnosis, sex, as well as needing to be alive at the time of death of the patient and to have some part of the colon intact five years prior to the diagnosis of the cancer of the patient. The criteria are extensive and valid and the authors' aim was to obtain 120 individuals. However they give the impression that after the 120 individuals were chosen, tight scrutiny of the criteria confined them to 102. Surely you would select your controls based on defining your criteria initially rather than reassessing the number of individuals chosen and excluding some that do not meet the "criteria".

Finally the results give a relative risk for which the reference is not clearly identifiable. One is left to assume that it is the relative risk of survival advantage having undergone a surveillance colonoscopy. Regardless of this, the confidence interval includes 1. Karlen *et al* go on to state that of those undergoing two or more surveillance colonoscopies the relative risk was 0.22 with a 95% confidence interval that is wider than the overall confidence interval for the relative risk of ever having a surveillance colonoscopy. This confidence interval also includes 1, and they state that somehow this indicates "a protective dose response relation".

The final comment in the results alludes to 10% of controls having undergone colectomy within five years prior to diagnosis of the cancer of the patient but we are not informed of the reasons why these patients underwent colectomy. It is important to know whether their colectomy was for colorectal cancer or failure of medical treatment to control their ulcerative colitis.

One is left disconcerted that, given the criticisms outlined earlier, the authors could still conclude that, "the main finding, although not statistically significant, indicates that colonoscopic surveillance may have a protective effect against death from colorectal cancer". Furthermore that this, "protective effect is even more pronounced if the patient underwent two or more surveillance colonoscopies, indicating a protective dose response relation".

This is clearly a negative study, and the statement that there is a "protective dose response relation" must be considered to be unfounded and biased.

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Cholecystokinin provocation tests

EDITOR,—The commentary by Al-Musawi and Williamson (*Gut* 1997;43:454-5) on our paper (*Gut* 1998;43:571-4) in the same issue suggests that there is still a place for cholecystokinin (CCK) provocation tests although the authors fail to provide any evidence to support their statement. Their criticism of our

paper relates to numbers of patients in subgroups and histology of the gall bladder, and they seem to have ignored the key message on outcomes after cholecystectomy in these patients as a whole. The only study they have quoted in support of their statement is Rhodes *et al*'s paper¹ which we have discussed in detail as proving that patients who were CCK negative had perhaps better symptom relief than CCK positive patients (89 v 67%). CCK does contract the gall bladder and may cause pain but this has no bearing on symptomatic outcome after cholecystectomy. This is what makes this test useless.

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Requiem for the cholecystokinin provocation test

EDITOR,—I read with interest the paper from Professor Johnson's group (*Gut* 1998; 43:571-4) questioning the value of the cholecystokinin (CCK) provocation test as a predictor of outcome following cholecystectomy in patients suspected of having acalculous biliary pain. The results of this study are predictable as in my experience tests of gall bladder function in this situation are not much better at outcome prediction than tossing a coin unless they are combined with a quantitative assessment of sphincter of Oddi function.

It is my practice when evaluating patients with suspected acalculous biliary pain to measure the gall bladder ejection fraction (GBEF) using a CCK stimulated HIDA (hydroxyindole diaminooacetic acid) scan. Patients with two separate GBEF values of <35% are offered endoscopic biliary manometry. Patients with normal manometry (basal pressure <40 mm Hg, mean peak wave pressure <140 mm Hg and contraction rate <9/min) of both biliary and pancreatic sphincters respond extremely well to cholecystectomy. Conversely, patients with abnormal manometry must be warned that sphincter of Oddi hypertension may result in post-cholecystectomy symptoms requiring treatment with calcium channel antagonists, botulinum toxin injection into the sphincter of Oddi or endoscopic sphincterotomy.

The modern biliary manometry catheter (Lehman catheter, Wilson Cook Ltd) with a distal aspiration channel has made endoscopic manometry of the sphincter of Oddi a safe procedure with an incidence of postprocedure acute pancreatitis of <5% even for patients with confirmed sphincter hypertension. Manometry of the hypertensive pancreatic sphincter should always be accompanied by short term pancreatic duct stenting as this reduces the incidence of acute pancreatitis in these patients dramatically.

I would suggest that the study from Smythe *et al* is incomplete without sphincter of Oddi function data and that we should not discard gall bladder function tests just yet.

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