1 Malbert C, Mathis C. Antropyloric modulation of transpyloric flow of liquids in pigs. *Gastroenterology* 1994; **107:** 37–46.
2 Horowitz M, Dent J. The study of gastric mechanics and flow: a Mad Hatter's tea party starting to make sense? *Gastroenterology* 1994; **107:** 302–6.
3 Tougas G, Anvari M, Dent J, Somers S, Richards D, Stevenson G. Relation of pyloric motility to pyloric opening and closure in healthy subjects. *Gut* 1992; **33:** 466–71.
4 Houghton L, Read N, Heddle R, Horowitz M, Collins PJ, Chatterton BE, *et al.* Relationship of the motor activity of the antrum, pylorus, and duodenum to gastric emptying of a solid-liquid mixed meal. *Gastroenterology* 1988; **94:** 1285–91.
5 Fone D, Horowitz M, Read N, Dent J, Maddox A. The effect of terminal ileal triglyceride infusion on gastroduodenal motility and the intragastric distribution of a solid meal. *Gastroenterology* 1990; **98:** 568–75.
6 Fraser R, Horowitz M, Maddox A, Dent J. Dual effects of cisapride on gastric emptying and antropyloroduodenal motility. *Am J Physiol* 1993; **264:** G195–201.
7 Fraser R, Horowitz M, Maddox A, Dent J. Postprandial motility and gastric emptying in gastroparesis – the effect of cisapride. *Gut* 1994; **35:** 172–8.
8 Sun W, Smout A, Malbert C, Edelbroet MAL, Jones K, Horowitz M, *et al.* Relationship between surface electrogastrography and antropyloric pressures. *Am J Physiol* (in press).
9 Heddle R, Dent J, Toouli J, Read N. Topography and measurement of pyloric pressure waves and tone in humans. *Am J Physiol* 1988; **255:** G490–7.
10 Camilleri M, Malagelada J, Brown M, Becker G, Zinsmeister A. Relation between antral motility and gastric emptying of solids and liquids in humans. *Am J Physiol* 1985; **249:** G580–5.
11 Prather C, Camilleri M, Thomforde G, Forstrom L, Zinsmeister A. Gastric axial forces in experimentally-delayed and accelerated gastric emptying. *Am J Physiol* 1993; **264:** G928–34.
12 Anvari M, Malbert C, Horowitz M, Jamieson G. Loxiglumide abolishes the effects of intraduodenal oleic acid on gastric motility and emptying in the pig. *Neurogastroenterology Motility* 1994; **6:** 181–8.
13 Camilleri M, Brown M, Malagelada J. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986; **91:** 94–9.
14 Camilleri M, Malagelada J. Abnormal intestinal motility in diabetics with the gastroparesis syndrome. *Eur J Clin Invest* 1984; **14:** 420–7.
15 Azpiroz F, Malagelada J. Gastric tone measured by an electronic barostat in health and post surgical gastroparesis. *Gastroenterology* 1987; **92:** 934–43.
16 Mearin F, Camilleri M, Malagelada J. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986; **90:** 1919–25.

Autoimmunity and chronic pancreatitis

EDITOR,—It was with considerable interest that I read the article by Jalleh *et al* (*Gut* 1993; **34:** 1452–7) on histocompatibility antigen expression in human chronic pancreatitis. The authors assessed the morphology of the pancreas and class I (HLA) and II (HLA-DR) histocompatibility antigen expression in surgical specimens obtained from a large series of patients with chronic pancreatitis (93 patients), comparing these with 10 patients undergoing surgical resection for the presence of neuroendocrine tumours of the head of the pancreas and with four patients with chronic obstructive pancreatitis. The authors showed that, in the specimens obtained from patients suffering from chronic pancreatitis: (a) the disease was focal in distribution; (b) in the early stage of the disease neither protein plugging of major ducts nor calcification of minute ducts were identified; (c) in the later stage of the disease sections comprised only a few residual epithelial elements together with nerves and vascular structures in dense fibrous connective tissue, together with focal calcifications; (d) in the early stage of the disease HLA class I expression by pancreatic exocrine epithelial cells was seen in 82% of chronic pancreatitis specimens, HLA class II in 66%, and both in 57%, whereas no major histocompatibility complex expression was identified in control specimens; (e) in the positive specimens expression was confined to ductal and ductular (inter and intralobular) epithelium with no staining of acinar cells; (f) T lymphocyte infiltration was significantly more prominent in chronic pancreatitis compared with control specimens. These data confirm those obtained in a study conducted by our team in Verona,[1] which showed increased HLA-DR expression in pancreatic specimens from patients with chronic pancreatitis, together with the presence of T lymphocyte infiltration foci, mainly surrounding the pancreatic ducts.

These reports seem to lend support to the hypothesis recently expounded by Cavallini[2] suggesting that primary (that is, non-obstructive) chronic pancreatitis is pathogenetically attributable to an obliterating primary inflammatory fibrosis of the main or secondary pancreatic ducts, or both. The fibrosis may be induced by active mediators released by T lymphocytes activated by aberrant expression of HLA. This phenomenon, which presents a patchy distribution, may be responsible for partial or total obstruction of the outflow of pancreatic juice, which in turn causes stasis facilitating the intraductal formation of protein plugs and the subsequent precipitation of calcium salts. Several experimental studies have, in fact, shown that partial obstruction of the pancreatic ducts alone is capable of causing the formation of intraductal stones in the dog[3 4] and in the rat.[5]

Although the data of the study by Jalleh *et al* need to be viewed with caution, as the authors themselves recommend, as aberrant ductal HLA expression may be secondary to an inflammatory phenomenon, we feel we should stress the fact that it was found in the early stage of the disease. Aberrant HLA expression was detected, in fact, in specimens with a histological picture compatible with early disease abnormalities. This mechanism therefore would seem to constitute an early pathogenetic factor in development of the disease.

As we see it, the abnormal HLA expression may result from a genetic defect. According to its expressivity, this genetic defect may be responsible, in the case of greater penetrance, for the juvenile forms of the disease (previously classified as hereditary) or, if there is less penetrance, for the classic form of disease, which manifest themselves above the age of 30 (adult chronic pancreatitis). Exogenous factors epidemiologically associated with chronic pancreatitis may contribute to HLA expression in genetically predisposed subjects (alcohol), or even accelerate the formation of intraductal stones (alcohol, smoking, diet) and thus have an impact on the progression of the disease. One last finding that should perhaps be emphasised is the lack of protein plugs or intraductal calcifications in specimens compatible with early disease abnormalities. This finding, together with a number of clinical features, such as the low incidence of calcifications in chronic alcoholic pancreatitis in the early stages of the disease, and biochemical considerations, such as the lack of disease in alcohol abusers with lower concentrations of lithostatin and the presence of protein microaggregates also in normal subjects, raises serious doubts as to the soundness of the pathogenetic hypothesis put forward by the Marseille school.[6] It is possible, as already postulated,[2] that the lithostatin abnormalities may be no more than an epiphenomenon related to chronic stasis secondary to ductal obstruction, parallel to the reduced acinar exocrine production of all the other proteic-enzymatic substances.

We believe that further, more thorough studies of an immunological and immunohistochemical type need to be conducted to confirm the possible autoimmune pathogenesis of primary chronic pancreatitis.

G CAVALLINI
L FRULLONI
V DI FRANCESCO
P BOVO
M FILIPPINI
B VAONA
Cattedra di Gastroenterologia, Università di Verona, Policlinico B go Roma, 37134 Verona, Italy

1 Bovo P, Mirakian R, Merigo F, Angelini G, Cavallini G, Rizzini P, *et al.* HLA molecule expression on chronic pancreatitis specimens: is there a role for autoimmunity. A preliminary study. *Pancreas* 1987; **2:** 350–6.
2 Cavallini G. Is chronic pancreatitis a primary disease of the pancreatic ducts? A new pathogenetic hypothesis. *Ital J Gastroenterol* 1993; **25:** 391–6.
3 Konishi K, Izumi R, Kato O, Yamaguchi A, Miyazaki I. Experimental pancreo-lithiasis in the dog. *Surgery* 1981; **6:** 687–91.
4 Sakakibara A, Okumura N, Hayakawa T, Kanzaki M. Ultrastructural changes in the exocrine pancreas of experimental pancreatolithiasis in dogs. *Am J Gastroenterol* 1982; **77:** 498–503.
5 Tanaka T, Ichiba Y, Miura Y, Itoh H, Doki K. Pathogenesis of chronic alcoholic pancreatitis. *Am J Gastroenterol* 1990; **85:** 1536–7.
6 Sarles H, Bernard JP. Lithostatin and pancreatic lithogenesis. *Gastroenterology International* 1991; **4:** 130–3.

Reply

EDITOR,—Thank you for the opportunity of replying to the letter by Cavallini *et al* in response to our paper describing the enhanced expression of major histocompatibility complex determinants in chronic pancreatitis. We agree with the correspondents' suggestion that predisposition of certain subjects to chronic pancreatitis may be congenital in origin. We do not yet have sufficient information, however, to suggest that the abnormal HLA expression we have identified in early chronic pancreatitis may be due, in itself, to a genetic defect. An alternative possibility is that enhanced HLA expression may be an epiphenomenon of the chronic inflammatory process and that the prime aetiology may lie in a genetic defect affecting another, although possibly related, molecule. For example, any of the endogenous molecules participating in the intracytoplasmic processing of cellular peptides or proteins (such as the heat-shock proteins) might be affected and hence permit inappropriate targets of immune recognition to develop within pancreatic epithelial cells.

Recently obtained data shortly to be published from our laboratory have clearly shown the enhanced and differential expression of transforming growth factor β_1 in human chronic pancreatitis.[1] These findings support the suggestion of Cavallini *et al* that potent mediators of an evolving inflammatory process probably promote the profound fibrosis characteristic of chronic pancreatitis while they are not aetiological factors. In this respect, we believe that enhanced expression