LETTERS TO THE EDITOR

Postprandial function in gastroparesis

EDITOR,—I read with great interest the article by Fraser *et al* (*Gut* 1994; **35:** 172–8) suggesting that the disturbed relation between antral, pyloric, and duodenal pressure waves is a major abnormality of postprandial function in gastroparesis, but showing no relation between gastric emptying and number of antral waves. The casual reader may conclude that Fraser's data refute some of our own work.[1-3] A more careful review of the experimental design and data analysis would suggest this is not the case. We had previously shown that the two hour postprandial antral motility index (that incorporates the number and amplitude of contractions) measured 1 cm proximal to the manometrically identified pylorus, significantly correlated with the rate constant for gastric emptying of solids[1] in health; considerably influenced the duration of the lag time and post-lag emptying rate for solids in gastroparesis[2]; and accounted for about 80% of the variance in emptying of solids in a pharmacological study that mimicked gastric dumping and gastric stasis.[3] Our hypothesis has been that, in the early postprandial period, the distal antral contractions set up the liquid shearing forces that triturate solids (hence influence on lag time) and that after emptying commences, these high amplitude contractions contribute to further trituration of the rest of the solid phase and propulsion of antral contents.

Fraser's experiment and analysis differ appreciably from ours: analysis of contractile activity starts from the end of the lag period, not from the end of meal ingestion, and stops 30 minutes later when a pharmacological intervention occurs. Moreover, Fraser *et al* used only the number of contractions at different sites without considering any role for amplitude or force of those contractions. We would suggest that evaluation of the postprandial handling of solids by the human stomach (a process that may take up to four hours even in healthy subjects) requires a longer period of analysis to prove or disprove the contribution of any specific contractile pattern and should include the initial phase of gastric retention, which is an integral part of the postprandial function of the stomach.

I do not believe that there is an enormous separation between the model proposed by the Adelaide group and our own hypothesis. The more proximal gastric contractions extending >6 cm are of interest and may conceivably represent fundic contractions, which may be further investigated by means of an intragastric barostat. But before we accept these as the propulsive force in the post-lag period, it is worth noting that in gastroparetic patients, the data of Fraser *et al* would suggest that these waves contribute to 20% of the variance in gastric emptying measured simultaneously. There is, however, a philosophical difference in our approaches to these studies of the relation between antropyloroduodenal contractions and gastric emptying. Dent's group has a major interest in the physiological contribution of each wave form and resistance to flow patterns; our own perspective has been more clinical as we try to understand the significance of regional dysfunctions in disease states and to obtain a surrogate estimate of the motor function of the stomach (that is, contractility and emptying). But, as detailed and careful studies are developed to shed light on the propulsive nature of gastric motor events, we ought to avoid the temptation of throwing out the baby with the bath water unless rigorous experimental design and analysis convincingly refute the significant body of evidence accumulated from previous studies.

MICHAEL CAMILLERI
Gastroenterology Research Unit,
Mayo Clinic,
Rochester, Minnesota 55905,
USA

1 Camilleri M, Malagelada J-R, Brown ML, Becker G, Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. *Am J Physiol* 1985; **249:** G580–5.
2 Camilleri M, Brown ML, Malagelada J-R. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* 1986; **91:** 94–9.
3 Prather CM, Camilleri M, Thomforde GM, Forstrom LA, Zinsmeister AR. Gastric axial forces in experimentally-delayed and accelerated gastric emptying. *Am J Physiol* 1993; **264:** G928–34.

Reply

EDITOR,—Professor Camilleri's letter raises a number of important issues relating to the optimal approach to an understanding of the mechanical factors responsible for normal and disordered gastric emptying in humans. While we do not wish to suggest that the manometric and radioisotopic methods used to evaluate gastric motor function by Professor Camilleri and his colleagues are not useful, it is our belief, based on insights from recent studies, that for substantial advances in this area to occur, important modifications to conventional strategies are now required.

Gastric emptying is a complex process that entails storage of ingesta, mixing with gastric secretions, grinding of solid food to small particles, and delivery of chyme into the small intestine at a rate designed to optimise digestion and absorption. Studies in which motility and transpyloric flow have been measured concurrently show that gastric emptying is predominantly pulsatile, rather than continuous, and that not all gastric contractions result in transpyloric flow.[1] The substantial second to second variations in both the volume and frequency of flow episodes reflect changes in the relations between motor events in different regions of the stomach and proximal small intestine.[1 2] We believe that both transpyloric and intragastric flow are critically dependent on patterns of lumen occlusion resulting from muscular contractions, because lumen occlusion prevents antegrade or retrograde flow.[3] Accordingly, we have placed considerable emphasis on definition and evaluation of the spatial and temporal organisation of patterns of lumen occlusion.[4-8] Though many distal stomach contractions have a peristaltic pattern of time of onset, this rarely translates into a peristaltic pattern of onset of contraction induced lumen occlusion.[2] This is distinctly different from the oesophagus. Studies using a sleeve sensor and a closely spaced side hole array to evaluate pyloric motility show that pressure waves localised to the pylorus probably play a significant part in the regulation of gastric emptying, in conjunction with other motor components.[4] A detailed analysis supports our view that the narrow (about 4 mm) zone of pyloric contraction cannot be defined adequately with conventional side hole manometric techniques alone.[9]

As no motor component can be considered to exert the dominant control, propulsive or retardant, over normal gastric emptying,[1 2] it is not unexpected that a measurement such as the motility index, combining both the amplitude and frequency of pressure waves in a single region of the stomach, accounts for only a comparatively small proportion of the rate of gastric emptying, as shown in elegant studies performed by Professor Camilleri *et al.*[10] The strong correlation seen in one study referred to by Professor Camilleri was derived from motor events recorded during stimulated and inhibited gastric emptying, which we believe limits the inferences that can be drawn.[11] We also do not wish to suggest that 'long' antral pressure waves are the only, or even the major, propulsive force in gastric emptying and have suggested that non-lumen occlusive contractions generated by the proximal stomach are probably important.[2 12] We believe that the impact of a specific motor pattern on transpyloric flow is best evaluated by correlating short term patterns of flow with these motor events rather than the use of motility indices derived from pressures recorded over long time intervals.

In patients with gastroparesis it is insufficient to focus on evaluation of antral motor function. While a reduction in fasting and postprandial antral pressure waves occurs frequently in these patients[13] this is by no means universal.[7] More importantly, a number of motor abnormalities in other regions (proximal stomach, pylorus, and small intestine) have been reported both by Professor Camilleri and his coworkers, and others.[14-16] Gastroparesis is therefore best considered to result from a spectrum of motor abnormalities, which include antral hypomotility, but also disordered proximal gastric tone, pyloric and proximal small intestinal function, and the organisation of motor events in different motor regions.[2] This is not surprising given the diverse aetiologies of delayed gastric emptying. Clearly we need correlative measurements that take all of these functional aspects into account to identify what is most important in any individual patient.

The mechanisms by which gastrokinetic drugs increase gastric emptying in patients with gastroparesis are poorly defined and the emphasis of our study was to investigate the effects of cisapride on antropyloroduodenal motility in patients with gastroparesis.[7] These drugs seem to act primarily by changing the organisation of gastric contractions to an expulsive pattern.

An optimal strategy for the evaluation of both normal and disordered gastric mechanics dictates that measurements of the temporal and spatial organisation of both lumen and non-lumen occlusive muscular contractions in different regions of the stomach and proximal small intestine and transpyloric flow are made concurrently, so that the relation between mechanical events and gastric emptying can be evaluated on a short term and, ideally, second by second, basis. Such an approach is now feasible in animals[1] and should be the goal of future studies in humans.[2]

R FRASER
M HOROWITZ
J DENT
Department of Medicine,
Royal Adelaide Hospital,
Adelaide,
South Australia

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