LETTERS TO THE EDITOR

Ileal pouch-anal anastomosis for Crohn's disease

EDITOR,—In his leading article (*Gut* 1998;**43**:303–8), Mr Phillips makes a plea for realistic comparisons between outcomes for pouch surgery in Crohn's disease with other restorative procedures for this disease, rather than comparisons with restorative proctocolectomy for other diseases, specifically ulcerative colitis. We agree that like comparisons are important in scientific analysis, but point out that such comparisons are confounded by the difficulties of accurate histological diagnosis in inflammatory bowel disease. In particular we should like to highlight the diagnostic confusion and unreliability of a change in diagnosis from ulcerative colitis to Crohn's disease based on the histological examination of the defunctioned rectum in ulcerative colitis.[1] Nearly all of the inflammatory changes of Crohn's disease have been described in the defunctioned colorectum in ulcerative colitis.[2] Any change from a diagnosis of ulcerative colitis to Crohn's disease must be based on a re-examination of the colectomy specimen and placed in context with the clinical history. The misdiagnosis of diverted ulcerative colitis, as Crohn's disease, will only add further to the confusion surrounding the debate on the role of the pelvic ileal reservoir in Crohn's disease.

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1 Deutsch AA, McLeod RS, Cullen J, *et al*. Results of the pelvic pouch procedure in patients with Crohn's disease. *Dis Colon Rectum* 1991;**23**:475–7.
2 Warren BF, Shepherd NA, Bartolo DCC, *et al*. Pathology of the defunctioned rectum in ulcerative colitis. *Gut* 1993;**34**:514–16.

A requiem for the cholecystokinin provocation test?

EDITOR,—We read with interest the study by Smythe *et al* (*Gut* 1998;**43**:571–4); however, we feel that on the basis of the data presented, the pronouncement of death for the test may perhaps be a little premature.

Firstly, despite the low sensitivity and specificity reported, the test still had positive and negative predictive values (66.7 and 57% respectively) which would be clinically useful in allowing patients to come to an informed decision regarding cholecystectomy.

Secondly, the authors conclude that there is no statistical difference between the positive and negative test groups in terms of their outcome after cholecystectomy. The relative benefit of the test expressed as the odds ratio is 2.7 with a 95% confidence interval from 0.7 (no benefit) to 10 (great benefit)—hence the authors cannot reach a conclusion with a study of this size regarding the usefulness of the test. We estimate that if the proportions of subjects in the various outcome groups remained the same, 148 subjects would be needed for the study to have 80% power with an odds ratio of 2.7. The ideal number of subjects for this study would depend on the size of difference in clinical outcome, which would be useful to detect. Obviously, if the true odds ratio is higher than 2.7 then fewer subjects would be required, but at a more realistic but still clinically useful odds ratio of less than 2.7 an even larger study would be necessary.

Thirdly, we obtained different figures for sensitivity, specificity and p value for the χ^2 test (with Yates' correction) of 75%, 47%, and p=0.26, respectively, with respect to symptomatic improvement after cholecystectomy—perhaps the authors' definition of these parameters was different to our own interpretation of their data.

Fourthly, the results of this study may not be applicable to a wider clinical setting. Cholecystectomy was performed on a highly selected group of subjects, after a variable time period and with the cholecystokinin provocation test result already known. It might have been more appropriate to offer all subjects cholecystectomy or to randomise them to management with or without knowledge of the test result.

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Reply

EDITOR,—We agree entirely with the concept that larger numbers in this study (as in any other) would yield narrower confidence intervals. In our study the cholecystokinin provocation test had low sensitivity and specificity (the use of Yates' correction is controversial) and we disagree that these positive and negative predictive values are clinically useful in counselling patients regarding outcome after cholecystectomy.

We also agree that a randomised blind study may be a more objective way of assessing the usefulness of this test; however, most patients in the study underwent cholecystectomy for symptoms and we have assessed symptomatic relief separately from cholecystokinin positivity. Indeed, most patients were given saline first (they were blinded to the infusion) and their symptoms recorded. We suggest that the comments raised by Campbell and colleagues do not detract from the fact that almost 50% of patients with acalculous biliary pain experience relief after cholecystectomy and the cholecystokinin provocation test is unable to predict those with good outcome.

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Measles virus and Crohn's disease

EDITOR,—We read with interest the view of Professor ter Meulen (*Gut* 1998;**43**:733–4) regarding the possible association of measles virus and Crohn's disease. We are in complete agreement with the author that current data available in the literature, mostly derived from serological, epidemiological and case control studies, are controversial and need to be investigated further. Professor ter Meulen proposes that the definitive answer to the problem of the involvement of measles virus in inflammatory bowel disease (IBD) would come from amplification of measles virus genome from IBD tissues by polymerase chain reaction (PCR) and then characterisation of the amplified DNA fragment by nucleotide sequencing. We would like to draw attention to published studies from several groups including ourselves and the IBD study group, who formulated the original measles hypothesis, which have tackled this issue using PCR but have not been mentioned by Professor ter Meulen in his article. These papers report highly sensitive measles specific RT-PCR systems that have been used to examine both colonic biopsy specimens (from both newly diagnosed and treated patients with Crohn's disease) and resection specimens, and have targeted different regions of the measles virus gene using primers corresponding to the N, F and H gene regions.[1–5] All have produced negative results.

Professor ter Meulen also suggests that lack of detection of measles virus in diseased tissues may be a result of low copy number of viral genes in infected cells. The sensitivity limits of the detection systems established by the groups mentioned earlier varied considerably. One group reported amplification of the target sequence from a single copy of the measles virus genome.[5] We successfully amplified RNA templates extracted from virus particles corresponding to about 10^{-3} pfu (plaque forming units) and applied approaches which potentially improved the sensitivity of the detection system by examining the amplified DNA products by Southern blotting or digoxigenin antibody assay.[2] Others also used different approaches to improve the assay sensitivity including enriching the measles virus RNA templates by oligonucleotide capturing from IBD specimens.[3] In our laboratory we were able to amplify measles virus RNA from a nucleic acid mixture extracted from control tissues including material from SSPE brain, colonoscopic biopsy samples spiked with measles virus, and from virus infected tissue culture fluid.[2]

This evidence supports the view that measles virus does not persist in IBD tissues and therefore probably is not involved in the aetiology or pathogenesis of Crohn's disease. In addition we suggest that lack of detection of measles virus sequence is not due to low copy numbers of viral genes but perhaps their complete absence.

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1 Afzal MA, Minor PD, Begley J, *et al*. Absence of measles virus genome in inflammatory bowel disease. *Lancet* 1998;**351**:646–7.
2 Afzal MA, Armitage E, Begley J, *et al*. Absence of detectable measles virus genome sequence in inflammatory bowel disease tissues and peripheral blood lymphocytes. *J Med Virol* 1998;**55**:243–9.
3 Chadwick N, Bruce IA, Schepelmann S, *et al*. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction. *J Med Virol* 1998;**55**:305–11.
4 Iizuka M, Nakagomi O, Chiba M, *et al*. Absence of measles virus in Crohn's disease. *Lancet* 1995;**345**:199.
5 Haga Y, Funakoshi O, Kuroe K, *et al*. Absence of measles virus genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. *Gut* 1996;**38**:211–15.

A UK training programme for nurse practitioner flexible sigmoidoscopy

EDITOR,—Duthie and colleagues (*Gut* 1998;**43**:711–14) have confirmed what we hoped, and wanted to believe, namely that properly trained nurses perform flexible sigmoidoscopy safely and effectively. This result offers the hope that we will be able to cope with increasing service demands but also addresses other important issues.

There seems to be a curious difference in our attitudes towards nurses and doctors in the performance of practical procedures. For the same patients and the same procedures we demand that nurses undergo formal training and assessment but do not insist on this for doctors. Where is the validated, agreed programme for medical and surgical trainees (or even consultants) who want to learn flexible sigmoidoscopy or indeed any other endoscopic procedure? There are excellent optional courses, outstanding teachers and willing students but no formal link to what goes on day to day in district general hospitals throughout the country. Calman has introduced the term "structured training", but evidence of structure is difficult to find. The curricula list procedures in which competence should be gained but make little mention of how these procedures should be taught or learned. We had previously been concerned that the omission was because we didn't know; it now seems that we do, but maybe believed structure and rigour were not necessary for doctors.

Just possibly we have come to believe that training is somehow inferior in status to education. This is to misunderstand the differences between the two activities. Rigorous formal training in practical procedures does not in any way negate the need for professional judgement, intuition and opinion but we no longer need reminding that the public are demanding proved, high levels of technical skill. The authors make the point that, "flexible sigmoidoscopy is a technical skill and. . .suitably motivated staff should be able to learn this technique." This is a fundamentally important point; skill is acquired by motivated learners who are prepared to practice and who have expert instruction and feedback. Some doctors or nurses will become more skilful than others because they are better motivated, practice harder and are better able to learn from experience. Many of our most skilful practitioners are self-taught, but for those starting now good coaching can probably shorten the time to a given level of competence. Skill itself cannot be taught but has to be learned. The concept of innate dexterity and talent is not supported by evidence[1] and is not conducive to the development of training. We would contest one point in this paper. The authors state that, "the theoretical, moral and legal information contained in a nurse endoscopy course was *obviously* (our italics) different to that required in a medical course." Surely the type and extent of information depend on the procedural experience and interest of the practitioner. With increasing technical and professional development the practitioner revisits the concepts at increasing levels of complexity. This is the essence of spiral curriculum.[2] Duthie and colleagues are to be congratulated for a truly structured nurse training programme that issues a challenge to doctors both in gastroenterology and other disciplines.

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1 Sloboda J. What is skill and how is it acquired? In: *Culture and processes of adult learning*. Routledge in association with The Open University, 1993:253–73.
2 Bruner J. *Towards a theory of instruction*. Cambridge, MA: Harvard University Press, 1966.

Gas and liquid reflux during transient lower oesophageal sphincter relaxation

EDITOR,—We read the paper by Sifrim *et al* (*Gut* 1999;**44**:47–54) with interest. Transient lower oesophageal sphincter relaxations (TLOSRs) have become widely accepted as the cause of most acid reflux episodes in health and disease. It is also accepted that TLOSRs are involved in the belch mechanism. This paper refutes our assertion that the majority of acid reflux events occur in healthy individuals in association with the venting of gas, based on pressure measurements in ambulant subjects.[1 2]

The current paper has shown that gas can be detected passing out of the stomach during TLOSRs. The authors found that only 18% of TLOSRs were solely gas reflux and nearly 60% of TLOSRs were associated with liquid reflux alone or neither the reflux of liquid or gas. This implies that spontaneous TLOSR occurs commonly and is not initiated by the fundal stretch "belch" mechanism. We wonder what exact teleological reason there can be for such a phenomenon.

The authors would suggest that in control subjects, acid reflux episodes are more common than simple belching. This seems contrary to most people's daily experiences and differs notably from our observations in normal subjects, where common cavity events with acid reflux are much less frequent than those without acid reflux. The pressure pattern of acid reflux alone, is quite different from the two types of common cavity event which we identified. Presumably all of this might be accounted for by the relative insensitivity of the authors' impedance system in the detection of small amounts of refluxed gas.

We remain unconvinced by the assertion that in normal subjects, acid reflux is a primary event, rather than one which accompanies the act of belching.

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1 Barham CP, Gotley DC, Miller R, *et al*. Pressure events surrounding oesophageal acid reflux episodes and acid clearance in ambulant healthy volunteers. *Gut* 1993;**34**:444–9.
2 Barham CP, Gotley DC, Mills A, *et al*. Precipitating causes of acid reflux episodes in ambulant patients with gastro-oesophageal reflux disease. *Gut* 1995;**36**:505–11.

Reply

EDITOR,—We thank Drs Barham and Alderson for their comments on our paper. The issue of the relation between gas reflux, as in belching, and acid reflux has been a thorny one and the subject of some interest over the past few years. We accept that our findings challenge the popular concept that, in normal subjects, acid reflux commonly occurs in the setting of and perhaps as a consequence of belching. Because transient lower oesophageal sphincter relaxations (TLOSRs) are the basic underlying event for both reflux of gas (as in belching) and liquid (as in acid reflux), and because belching is considered a normal physiological process, it is natural to presume that, on occasions, acid sometimes escapes along with the gas.

The observations that have fuelled this conclusion, however, have been based on some assumptions about the interpretation of pressure tracings. In their paper on the mechanism of reflux in ambulant healthy subjects, Barham and colleagues assumed that the presence of an abrupt rise in intra-oesophageal pressure preceding the drop in pH indicated the reflux of gas. No direct detection of intra-oesophageal gas was undertaken. In our study we have used intraluminal impedance to detect gas, and pH to detect acid. It is clear from the impedance measurements that common cavities can occur in the absence of any detectable gas. Although we acknowledge that technical limitations such as the sampling rate may have limited the sensitivity of detection of rapidly moving small quantities of gas, intraluminal impedance is well capable of detecting substantial volumes of gas such as those that occur during belching. Therefore, we believe that our observations have a distinct methodological advantage over those of Barham and colleagues with regard to the patterns of gas reflux during TLOSR.

It is possible, therefore, that the apparent discrepancy between our findings and those of Barham *et al* may result from the technical limitations of their study. We found that gas accompanied liquid reflux on almost half (47%) of the acid reflux episodes, compared with 69% of acid reflux episodes that were associated with belching—that is, associated with a common cavity. Firstly, some of the common cavities observed by Barham *et al* may have been pure liquid reflux. Secondly, they were unable to determine accurately the timing of the liquid and gas retroflow. It is possible that some of the presumed gas reflux actually started after the onset of the liquid reflux, as we observed in our study.

Drs Barham and Alderson have interpreted our findings as implying that "spontaneous TLOSR occurs commonly and is not initiated by the fundal stretch 'belch' mechanism". Our findings do nothing of the sort. The gastric fundus can be stretched or distended by liquids and solid meals just as

well as by gas, and all of these stimuli, as well as intragastric balloons, have been shown to increase the rate of TLOSRs. Intragastric gas is not essential for triggering TLOSRs. There is a low rate of TLOSR during fasting. The mechanisms responsible for this have not been properly defined but may well involve small degrees of fundal distension from the gastric air bubble that is usually present even in the "empty" stomach.

Although we believe that our data and their interpretation are valid, it is also important to acknowledge that there are other differences between our study and that of Barham *et al* that could have influenced the findings. Firstly, our study was performed in stationary sitting subjects, as opposed to ambulatory subjects. Secondly, the majority of our TLOSRs occurred in the postprandial period whereas those in the study by Barham *et al* were gathered from substantial interdigestive as well as postprandial periods. The impact of ambulation on patterns of gas and liquid reflux has still to be studied.

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BOOK REVIEW

The Pancreas. Volumes 1 and 2. Edited by Beger HG, Warshaw AL, Buchler MW, Carr-Locke DL, Neoptolemos JP, Russell C, Sarr MG. (Pp 1509; illustrated; £295.00.) UK: Blackwell Science Ltd, 1998. ISBN 0 86542 420 9.

Imagine the task: seven editors coordinating manuscripts from 222 contributors, two thirds of whom are surgeons and most are professors. They have synthesised a landmark reference book of 1509 pages which seems destined to become the bible of the pancreas.

I chose a 12 hour return rail journey to attend the Pancreatic Society to review this monumental book. I was well rewarded and even though I had listened to the delivery of many papers at the cutting edge of pancreatic research at the scientific meeting, *The Pancreas* was well up to date probably because the editors had asked for an update just prior to publication. It would be fruitless to list the contents of this book because all aspects of pancreatic disease, physiology and anatomy are covered in very great detail.

The one obvious hallmark of this book is the evidence base with which the authors have been encouraged to back-up their contribution. Most chapters incorporate a battery of several hundred citations from the literature and many include well reasoned debate on difficult areas of management of pancreatic disease. Inevitably this results in some overlap between chapters but this enriches the debate in difficult areas. For instance utilisation of different imaging modalities is controversial. Thus the reader will find different opinions regarding use of computed tomography (CT) (chapter 15), spiral CT angiography (chapter 19), endoscopic ultrasound (chapter 102), and laparoscopy (chapter 107). Laparoscopic ultrasound has not been discussed and perhaps this is an omission which will undoubtedly find its way into the next edition. Similarly the surgeon will find a magnificent array of information, diagrams and pictures regarding surgical management with extensive coverage of the Japanese staging classification with pictures of the primary lymph node groups and detailed descriptions of the techniques used for resection, ranging from simple enucleation techniques to the complex duodenum preserving operations for chronic pancreatitis. The publishers have played no small part in this clarity because they have provided uniform illustrations throughout the text which are beautifully clear and understandable cartoon images in black and white.

The pearls from this book include the extensive and balanced account of biliary acute pancreatitis, a thoroughly realistic account of endoscopic treatment of chronic pancreatitis, an exhaustive coverage of tumour markers, and a chapter which should be read by all physicians on indications for surgical resection.

The only difficulty I have with this book is struggling with my conscience to retain it in my personal library rather than give it to our medical library as a reference book which is where it belongs. Space prevents me from telling you where it will ultimately reside!

A N KINGSNORTH

NOTES

European Pancreatic Club

The annual meeting of the European Pancreatic Club will be held at the Hotel Seminaris, Lüneburg, Germany, on 28–31 July 1999. Further information from: Professor Paul Georg Lankisch, Municipal Hospital, Division of Medicine, Bögelstrasse 1, D-21339 Lüneburg, Germany. Tel: +49 4131 77 2240; Fax: +49 4131 77 2245; Email: lankisch@uni-lueneburg.de

Frontiers in Pancreatic Physiology

A symposium on Frontiers in Pancreatic Physiology will be held at the Hotel Seminaris, Lüneburg, Germany, on 31 July to 1 August 1999. Further information from: Professor Maynard Case, School of Biological Sciences, The University of Manchester, G. 38, Stopford Building, Oxford Road, Manchester M13 9PT, UK. Tel: +44 (0)161 275 5406; Fax: +44 (0)161 275 5600; Email: rmcase@man.ac.uk

CORRECTION

Minor errors occurred in table 1 of the paper by Halasz *et al* (*Gut* 1999;**44**:274–8) and hence appear throughout the text. The correct figures (given below) do not affect the significance levels quoted nor the interpretation of the data. The authors regret any inconvenience these errors may have caused.

- p274, abstract, left hand column, line 24: "14 (24)%" should read "13 (22%)"; line 27: "seven of ten" should read "six of nine";
- p275, materials and methods, left hand column, lines 5 and 6: ". . .for 10 of the 58 patients that had GBV-C RNA or. . ." should read ". . .for nine of the 58 patients that had GBV-C RNA and/or. . ."; right hand column, line 35: "To simplify. . .SD." should read ". . .SD. Only samples which were reactive in all three independent runs were considered to be positive."; line 58: "14 (24)%" should read "13 (22)%";
- p276, results, legend to fig 1, line 5: "The horizontal. . . (LTx)." should read ". . . (LTx). GBV-C E2 EIA data obtained from the first run have been plotted only as an example of an EIA outcome. However, all samples were run in triplicate and only those reactive in all three runs were regarded as true positive. Consequently some positive points in the figure were scored as negative in the final evaluation."; right hand column, line 7: "(4/27; table 1)" should read "(3/27; table 1)";
- p277, left hand column, line 30: "14" should read "13"; line 33: "Three" should read "Two"; discussion, right hand column, line 12: "36%" should read "34%"; line 52: "patient FH4" should read "patient FH7".

Table 1 Presence of GBV-C RNA and E2 antibodies in 58 patients with fulminant hepatic failure sampled after admission to hospital and initiation of treatment. In addition, samples were obtained from nine patients on first admission to hospital and before treatment. Also given is the analysis of GBV-C E2 antibodies in 43 healthy subjects

Aetiology	No of patients	No of patients (%) with GBV-C			No of patients out of those tested with known GBV-C seroconversion after admission	
		RNA	Antibodies	Markers	RNA	Antibodies
Unknown	27	5 (19)*	3 (11)	7 (26)†	3/4	—†
Viral	6	0	2 (33)	2 (33)	—	—
Drug related	14	2 (14)	3 (21)	5 (36)	1/1	—
Miscellaneous	11	2 (18)	5 (45)*	6 (55)††	0/1††	2/4††
Total	58	9 (16)**	13 (22)*	20 (34)	4/6	2/4
Healthy subjects	43	†††	2 (5)	—	—	—

*p<0.05 compared with the healthy subjects (Fisher's exact test).
**p<0.01 compared with the healthy subjects (Fisher's exact test).
†Patient FH5 had GBV-C E2 antibodies at admission and became positive for GBV-C RNA after treatment. The sample obtained after treatment became exhausted prior to antibody analysis.
††Patient FH7 was positive for both GBV-C RNA and GBV-C E2 antibodies in samples obtained before and after treatment of FHF which presented 13 days after a bone marrow transplant.
†††Frequency of GBV-C RNA (3/100; 3%) in healthy Swedish subjects.[21]