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 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. Nearly all of the inflammatory changes of Crohn’s disease have been described in the defunctioned colorectum in ulcerative colitis. Any change from a diagnosis of ulcerative colitis to Crohn’s disease must be based on a re-examination of the colorectal 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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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 to 10 (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 will 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 χ2 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 routine 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 approaches which potentially improved the sensitivity of the detection system by examining the amplified DNA products by Southern blotting or digoxigenin antibody assay. Other authors also used different approaches to improve the assay sensitivity including enriching the measles virus RNA templates by oligonucleotide capturing from IBD specimens. 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. This evidence supports the view that measles virus RNA 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 in diseased tissues may be a result of low copy number of viral genes in infected cells and the lower 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. We successfully amplified RNA templates extracted from virus particles corresponding to about 100 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. Other authors also used different approaches to improve the assay sensitivity including enriching the measles virus RNA templates by oligonucleotide capturing from IBD specimens. 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.

This evidence supports the view that measles virus RNA does not persist in IBD tissues and therefore probably is not involved in the aetiology or pathogenesis of Crohn’s disease.

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Measles virus and Crohn’s disease

Editor,—We read with interest the view of Professor ter Meulen (Gut 1998;43:734–5) 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 confirmation of the amplification 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 RTPCR systems that allow reexamination of confined 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 regions.‡ 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 and the lower 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.‡ We successfully amplified RNA templates extracted from virus particles corresponding to about 100 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. Other authors also used different approaches to improve the assay sensitivity including enriching the measles virus RNA templates by oligonucleotide capturing from IBD specimens.‡ 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.

This evidence supports the view that measles virus RNA does not persist in IBD tissues and therefore probably is not involved in the aetiology or pathogenesis of Crohn’s disease.

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S Ghosh
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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 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 we demand of nurses in ambulant health services. For the majority of acid reflux events occur in health and disease. It is also accepted that lower oesophageal sphincter relaxations (LOR) are associated with belching—that is, associated with gas. It is clear from the impedance measurements that common cavities can occur in the absence of any detectable reflux. We found 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 detection of intra-oesophageal gas was under- scored by the fundal stretch ‘belch’ mechanism. Our findings do nothing of the sort. 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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Gas and liquid reflux during transient lower oesophageal sphincter relaxation

Editor,—We read the paper by Sifrim et al (Gut 1998;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 belching of gas, based on pressure measurements in ambulant subjects. 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 2/3 of TLOSRs were associated with liquid reflux alone or neither the reflux of liquid or gas. This implies that spontaneous TLOS 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. C P BARHAM

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 Max Ward, 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

BOOK REVIEW

The Pancreas. Volumes 1 and 2. Edited by Beger HG, Warshaw AL, Buchler MW, Carr-Locey DL, Neoptolemos JP, Russell C, Sarr MG. (Pp 1509; illustrated; £295.00.)

Imagine the task: seven editors coordinating manuscripts from 222 contributors, two thirds of whom are surgeons and many 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 endo-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 and exocrine pancreatitis, a thoroughly realistic account of endoscopic treatmen 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, Bögelsstraße 1, D-21339 Lüneburg, Germany. Tel: +49 4131 77 2240; Fax: +49 4131 77 2245; Email: lankisch@uni-luenburg.de

Table 1 Presence of GBV-C RNA and E2 antibodies in 58 patients with fulminant hepatic failure

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>No of patients (%) with GBV-C</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td>Unknown</td>
<td>27</td>
</tr>
<tr>
<td>Viral</td>
<td>6</td>
</tr>
<tr>
<td>Drug related</td>
<td>14</td>
</tr>
<tr>
<td>Miscellaneus</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>43</td>
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</table>

<table>
<thead>
<tr>
<th>No of patients out of those tested with known GBV-C seroconversion after admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBV-C RNA</td>
</tr>
<tr>
<td>3/4</td>
</tr>
<tr>
<td>1/1</td>
</tr>
<tr>
<td>1/4†</td>
</tr>
<tr>
<td>4/6</td>
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</table>

*<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 FH3 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 FH3 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 (5/100; 3%) in healthy Swedish subjects.
Ileal pouch-anal anastomosis for Crohn's disease

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