LETTERS TO THE EDITOR

Aminosalicylate as prophylaxis for Crohn's disease

EDITOR,—We read with interest the recent clinical alert commentary by Rutgeert et al (Gut 2001;48:452–53) analysing the recently published study by Lochs and colleagues.1 Lochs et al concluded that compared with placebo, 18 months of treatment with high dose Pentasa (mesalazine 4 g/day) made no difference to postoperative recurrence rates in patients with Crohn's disease involving the small intestine and colon or colon alone (26.3% vs 25.6% for mesalazine and placebo, respectively). We feel that this study raises many new questions with regards to the role of 5-aminosalicylate (5-ASA) formulations in the prevention of postoperative Crohn's disease. Furthermore, the study is not as negative as it first appears. Although in general terms the trial is well designed and includes a large number of patients (n=318), analysis of the results still presents a number of problems. Firstly, Lochs et al did not attempt to subgroup patients on the basis of the type of operation performed. This may be critical. It has been shown that the type of anastomosis performed at operation in Crohn's patients profoundly affects the efficacy and pharmacokinetics of 5-ASA formulations, possibly as a result of differential effects on intestinal transit time. Secondly, for a number of reasons, including all disease sites (small and large bowel) in a single analysis may disguise subgroups of patients who benefit from treatment. In fact, the study of Lochs et al provides extremely encouraging information with regard to the effects of mesalazine on postoperative recurrence in patients with disease limited to the small bowel. This subgroup of patients (37.8% of patients included; n=124) showed a significant improvement in relapse rates with mesalazine treatment (21.8% vs 39.7% for placebo and mesalazine, respectively; p=0.002), a fact overshadowed in the overall analysis. This may reflect differential effects in disease behaviour between patients or may raise questions with regard to the appropriateness of using the same 5-ASA preparation for all disease sites. The extremely high dropout rate in the study of Lochs et al is also worthy of comment. A total of 131 of 318 randomised patients were protocol violators. Meta-analysis of previous randomised controlled trials concerned with 5-ASA use in the prevention of postoperative relapse report much lower dropout rates (64/304).1

We feel that the data of Lochs et al merit further trials in this area. Future trials need to focus on defined subgroups of operations and on subgroups of patients with Crohn's disease affecting different bowel sites. The use of single drug formulations appropriate to the sites affected would obviously be desirable and might permit lower doses to be used with consequent lower patient dropout rates. Such studies would be a logistic challenge requiring a multicentre design to recruit sufficient numbers of patients. However, we feel it would be a worthwhile exercise as postoperative recurrence is a devastating complication in Crohn’s disease and it would be a shame to miss any relatively simple and non-toxic opportunity to avoid it.

A QASIM J SERRY C A O’MORRAN Adelaide and Meath Hospital, Incorporating the National Children’s Hospital, Talbot, Dublin, Ireland

Correspondence to: Dr A Qasim, AMNCH, Talbot, Dublin, Ireland. ashardar@hotmail.com


Probiotics in IBD

EDITOR,—We read with interest the therapy update by Shanahan (Gut 2001;48:609). This is an excellent summary of the potential role of bacteria both in the pathogenesis and treatment of inflammatory bowel disease (IBD). The author is correct in stating that our knowledge of the composition and interactions of endemic gut bacteria remains limited. However, the increasing data showing a reduction in inflammation and symptoms in experimental and clinical enterocolitis treated with probiotics1 strengthens the hypothesis that bacteria are involved in the aetiology of IBD.2 It is indeed unlikely that a single probiotic will be effective in the general patient with IBD as different bacteria may be contributing to the persistence of intestinal inflammation in individual patients. Similarly, different species of probiotic bacteria may be the dominant protective bacterial species in each patient. Therefore, as the author rightly comments, a single probiotic is unlikely to be equally effective in all patients.

We have shown for the first time that treatment with Lactobacillus species 299 stabilises the gut mucosal barrier in patients with ulcerative colitis and in the interleukin 10 knockout mouse model of colitis.1 There was also a reduction in laboratory markers and indices of disease activity in ulcerative colitis patients.3 These findings suggest that probiotic therapy, by reducing intestinal inflammation, results in stabilisation of the gut mucosal barrier and a consequent reduction in the systemic inflammatory response in patients with ulcerative colitis. Further research is required to elucidate the mechanisms by which these bacteria reduce inflammation and improve symptoms in patients with IBD.

R J KENNEDY K R GARDINER Department of Surgery, Queen’s University of Belfast, Belfast, UK

Correspondence to: Mr R J Kennedy, Department of Surgery, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, UK.

2 Sartor RB. Review article: Role of the enteric microflora in the pathogenesis of intestinal inflammation and arthritis. Pharm Ther 1997;11:17–23.

Probiotics in Crohn's disease

EDITOR,—In their “therapy updates”, Professors Shanahan (Gut 2001;48:609) and Professor Colombel et al (ibid 2000;48:649) respectively, addressed the issues of “probiotics in IBD” and of “antibiotics in Crohn’s disease”. I would like, shuffling the titles of their articles, to add a few comments on “antibiotics in Crohn’s disease”. Colombel et al pointed out the importance of intestinal flora in the pathogenesis of Crohn’s disease and the therapeutic role that antibiotics can play in this disorder.

An alternative approach to the problem would be to alter the enteric microflora by employing probiotics, in the attempt to achieve therapeutic benefits without the side effects of antibiotics. Oddly enough, neither Colombel et al nor Shanahan mentioned this possibility, the latter limiting his bibliographic references to studies carried out in ulcerative colitis and pouchitis.

As both authors omitted to mention it, I feel obliged to quote our own study with Saccharomyces boulardii, carried out in patients with Crohn’s disease.1 In a randomised trial, 32 patients with Crohn’s disease in remission were allocated to maintenance treatment with either mesalazine 3 g daily or mesalazine 2 g daily plus a preparation of Saccharomyces boulardii, two 500 mg capsules in the morning. Clinical relapses at six months were found significantly less frequently in the group who, in addition to standard mesalazine maintenance, had been taking the probiotic agent.

Further to that study, as the product is rather expensive and is not reimbursed by our National Health Service, we attempted to decrease the cost of such a therapy by reducing either the frequency of the product intake (only the first two weeks of each month) or the daily dose of the probiotic (one 500 mg capsule in the morning instead of two). Of course, no matter what, unpublished observations seem to suggest that a lower dose may be equally effective, provided that Saccharomyces boulardii is taken every day. Clearly, additional studies are needed before advising the use of Saccharomyces boulardii or other probiotics in the long term management of Crohn’s disease. As Colombel et al reminded us, patients should be straitened according to pathologic type,2 the therapeutic effect of probiotics being
probably more pronounced when the inflammatory features prevail over the fibrotic process. On the other hand, Shanahan rightly observes that it is unlikely that a single probiotic is suitable for all patients. *Saccharomyces bouardi* is a promising agent in the maintenance treatment of Crohn’s disease but its effects in ulcerative colitis remain unknown, being currently under investigation. Probiotic cocktails may well be the right solution, but the products successfully employed in pilot studies—excluding Crohn’s disease, so far—are not commercially available and we have no idea of their price until they are launched in the market.

M GUSLANDI
Gastroenterology Unit, S Raffaele University Hospital, Via Olgettina 60, 20132 Milan, Italy guslandi.mario@tiscali.it


Survey of informed consent for endoscopy

**Editor,—**Informed consent is an integral part of good medical practice. The recently published Department of Health (DoH) reference guide to consent for examination or treatment lays out the most up to date recommendations for obtaining consent.1 It includes guidance relating to the timing of consent and the provision of sufficient information for valid consent. For gastroenterologists, consent for procedures usually relates to endoscopy, and guidelines for this have also been produced by the British Society of Gastroenterology.2 It is not clear how well endoscopists and endoscopy units perform in relation to these guidelines, and the guidelines themselves acknowledge the practical difficulty of achieving some of the standards. To attempt to assess current practice, a questionnaire was used to obtain information from endoscopy units.

A standard anonymous questionnaire was sent to the ward manager of each of the endoscopy units in the North West region of the UK as a whole. It clearly demonstrates widespread variation in practice, both between individual units and to a lesser extent between individual doctors working at the same units. Present consent procedures appear to fall short of the ideal set out by the DoH guide and the GMC, particularly with regard to information about procedural risk, involvement of trainees in service provision, and allowing patients sufficient time to make informed decisions.1 The DoH guide recommends that consent should be sought well in advance and that information should be given about “significant” risks. Arguably the amount of information given about such matters as procedural risk may vary on a patient by patient basis. In a busy working environment, extra time spent explaining procedures may not appear productive but in the longer term will safeguard against complaints and even litigation.

**Table 1 Results of questionnaire**

<table>
<thead>
<tr>
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<th>Yr (%)</th>
<th>No (%)</th>
</tr>
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<tbody>
<tr>
<td>Is a standard method of obtaining consent for endoscopy used by all consultant firms?</td>
<td>13 (76%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Are patients routinely given written information prior to arranging for endoscopy?</td>
<td>16 (94%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>If written information is given does this include information about procedural risk?</td>
<td>11 (65%)</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Are patients routinely advised that trainees (e.g. SHOs/SpRs) may perform procedures?</td>
<td>7 (41%)</td>
<td>10 (59%)</td>
</tr>
<tr>
<td>Are patients fully informed about procedures 24 hours or more before the procedure?</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Do patients sign the actual consent form immediately prior to the endoscopy?</td>
<td>16 (94%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Is there an opportunity for patients to ask any last minute questions immediately before the procedure?</td>
<td>17 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Do you use procedure specific consent forms (i.e. separate forms for gastroscopy, colonoscopy, and ERCP)?</td>
<td>1 (6%)</td>
<td>16 (94%)</td>
</tr>
<tr>
<td>Final aspect of same system of obtaining consent available for inpatients as outpatients?</td>
<td>12 (71%)</td>
<td>5 (29%)</td>
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**Why measure thiopurine methyltransferase activity? Direct administration of 6-thioguanine might be the alternative for 6-mercaptopurine or azathioprine**

**Editor,—**6-Mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are effective in inflammatory bowel disease (IBD), mainly by their active 6-thioguanine (6-TG) metabolites. Efficacy and also myelotoxicity of 6-MP and AZA seem to be related to the 6-TG levels achieved. Instead of activation to 6-thioguanine nucleotides, 6-MP and AZA can be inactivated to 6-mercaptopurine (6-MPP) by the enzyme thiopurine methyltransferase (TPMT). High interindividual variability in TPMT activity is known. Therefore, measuring TPMT activity could be used to adjust the dose of 6-MP or AZA to reduce myelotoxicity. However, levels of 6-MPP formed by TPMT seem to correlate with toxicity.

The issue in the commentary by Sandborn (Gut 2001;48:591–2) was rational dosing of AZA and 6-MP. However, we would like to focus on direct administration of the active metabolite 6-TG. In a recent pilot study in IBD, patients treated with 6-MP methylated metabolites detected.3 6-TG dosing is feasible without measuring TPMT activity.

Following intravenous administration of 6-TG, pharmacokinetic behaviour is biphasic: a distribution half life of 15 minutes followed by a terminal half life of 11 hours. Oral absorption of 6-TG is approximately 30%. Administration by oral suspension is possible in which the suspension is stable for almost three months.4 6-TG tablets (Lanvis) have been available in our country since 1975 and registered for the treatment of acute and chronic myeloid leukaemia and acute lymphatic leukaemia.

We have started a prospective study of AZA or 6-MP in IBD patients with recurrent adverse events. The design is a non-randomised open label pilot study in which the drug to be used is that currently administered. Patients, who have not tolerated previous treatment or who have adverse events, will be randomised to 6-TG or AZA or 6-MP in multi-centre, prospective, randomised trials, leading up to FDA registration approval in the USA and Europe.

The aim of the study is to obtain a clearer understanding of adverse events in combination with 6-TG serum levels in IBD, especially in patients with a history of skin rashes, fever, and pancreatitis related to AZA and 6-MP. Our first results are promising. However, we must evaluate 6-TG versus AZA and 6-MP in multicentre, prospective, randomised trials, leading up to FDA registration approval in the USA and Europe. Our major concern is that Glaxo-Wellcome is not interested as the drug is out of patent, similar to the situation with beclomethasone for IBD in the past.5

**References**

3 Dubinsky MC, Hassard PV, Abreu MT, et al. Thioguanine (6-TG): a therapeutic alternative for the longer term will safeguard against complaints and even litigation.

The DoH guide recommends that consent should be sought well in advance and that information should be given about significant risks. Arguably the amount of information given about such matters as procedural risk may vary on a patient by patient basis. In a busy working environment, extra time spent explaining procedures may not appear productive but in the longer term will safeguard against complaints and even litigation.

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Interpretation of liver biopsy findings depends very much on clinicopathological correlation. In some cases, a liver biopsy may be taken in order to reach a primary diagnosis. In other cases, for example a patient with chronic hepatitis, a diagnosis may already have been made and the biopsy is taken for other reasons, in this instance to assess the necroinflammatory grade and fibrosis stage.

This book, which is written by a pathologist (Gary C Kanel) and a physician (Jacob Korula), provides a practical approach to the assessment of liver biopsies and the correlation of histological changes with relevant clinical findings. The book begins by describing a method for the systematic evaluation of findings. The book begins by describing a method for the systematic evaluation of findings. The more experienced liver pathologist faced with a difficult specimen may find the lists of differential diagnoses useful on occasions. Those seeking a more detailed understanding of liver pathology and pathogenetic mechanisms will still wish to have access to one of the larger standard liver pathology texts as a reference manual.

S HUBSCHER


This is a new comprehensive textbook covering upper gastrointestinal surgery other than HPB but also including all small intestine which is a frequently forgotten part of the gastrointestinal tract coming as it does between the colorectal and upper gastrointestinal surgeons. It is an extremely comprehensive and inclusive textbook which is both its strength and in other senses its weakness. There is no real subject in the oesophagus, stomach, duodenum, and small bowel which is not covered to some degree within the text. In such a large text however, the text itself varies with the bibliography, in some cases being up to the late 1990s but in others being really the early 1990s. The text is well laid out apart from the colour plates which are put at the beginning rather than as inclusive parts of the text, with clear diagrams, tables, and figures. It manages to combine well what is in essence a textbook of surgery along with a textbook of operative surgery. Each chapter is well referenced. Some of the best chapters in fact are those on miscellaneous conditions or on the rarities. Such a comprehensive text is invaluable to the junior resident who is seeking to write up a case report in what is perceived as an unusual condition.

In some ways the weaknesses of this text stem from the comprehensive nature of the text. Oesophageal cancer and gastric cancer are covered as separate entities. It is now generally recognised that in the western world cancer of the oesophagus and stomach in 75% of cases is an adenocarcinoma found within 5 cm of the gastro-oesophageal junction rather than either purely oesophageal or purely gastric. The separation of these two diseases into two separate chapters in separate parts of the book is a weakness and tends to underestimate this particular problem. Barrett’s oesophagus is also dealt with in a rather cursory fashion. Barrett’s oesophagus and its management as well as Barrett’s cancer as a major complication is currently one of the most popular issues of upper gastrointestinal surgery. Perhaps in future editions this disease can be looked at as a separate entity that bridges the stomach and oesophagus. There is also increasing awareness of the importance of quality of life issues, particularly in the treatment of patients with cancer and this, although dealt with, will require expansion.

The chapters on peptic ulceration are now, to a large degree, of almost historical interest. The subject is covered extensively but with the recognition of Helicobacter pylori and non-steroidal anti-inflammatory drugs and their pharmacological management, the role of surgery for chronic peptic ulcer has all but disappeared. It would be interesting to know when anybody last performed a highly selective vagotomy. The chapters for the surgical treatment of chronic peptic ulcer are also of historic interest only, as is the discussion about the most appropriate way to do a highly selective vagotomy. Gastric secretion tests, other than in patients with suspected Zollinger-Ellison syndrome, again are now a thing of the past.

These minor considerations apart, this is a well written, well referenced, and well illustrated textbook. I am sure it will have a place in all major libraries and libraries within individual departments. It is unlikely to appeal however to the individual, largely on the basis of its size and cost, and the ready availability of smaller but focused textbooks on the upper gastrointestinal tract and oesophageal disease which by their nature and size tend to be more up to date and focus on controversial issues such as investigation and management of cancer, palliation of malignant disease, multidisciplinary approach to malignant disease, the combination of surgery and oncology, issues of quality of life, management of gastro-oesophageal reflux, surgical versus medical, and the role of surgery in the treatment of peptic ulceration, which is now largely the simple under running of bleeding ulcers and closing of perforations, backed up by full pharmacological treatment with triple therapy.

These factors are all covered in the textbook but are missed by the full and thorough comprehensive nature which still tends to emphasise possibly a more aggressive surgical approach.

R C MASON

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2002

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2001 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in
March 2002. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

Hopkins Endoscopy Prize 2002
Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2002 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2002. Applications (TEN COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2001.

41st St Andrew's Day Festival Symposium on Therapeutics
This will be held on 6–7 December 2001 in Edinburgh, UK. Further information: Ms Eileen Strawn, Symposium Co-ordinator. Tel: +44 (0)131 225 7324; fax: +44 (0)131 220 4393; email: e.strawn@rcpe.ac.uk; website: www.rcpe.ac.uk

50th Anniversary of the First Right Hepatectomy: from Resection to Donation
This event will be held on 14–15 December 2001 in Paris, France. Further information: Michele Centonze Conseil, 6 bis rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58; email: mail@m-centonze-conseil.com; website: www.m-centonze-conseil.com

GI Malignancies Can be Prevented and Treated: from the Bench to the Bedside
This international meeting will be held on 15–20 January 2002 at the Dead Sea, Israel. Further information: Secretariat, GI Malignancies, PO Box 29041, Tel Aviv 61290, Israel. Tel: +972 3 5175150; fax: +972 3 5175155; email: gi@targetconf.com
Why measure thiopurine methyltransferase activity? Direct administration of 6-thioguanine might be the alternative for 6-mercaptopurine or azathioprine

D de JONG, C J J MULDER and A A van SORGE

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