Aminosalicylate as prophylaxis for Crohn's disease

EDITOR,—We read with interest the recent clinical alert commentary by Rutgeerts (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 relapse. 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.2 Second, 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 differences 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.3 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).4 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
C L SERRY
C A O’MORRIN
Adelaide and Meath Hospital, Incurring the National Children’s Hospital, Tallaght, Dublin, Ireland

Correspondence to: Dr A Qasim, AMNCH, Tallaght, Dublin, Ireland.
asghard@hotmail.com


Probiotics in IBD

EDITOR,—We read with interest the therapy update by Shanahan (Gut 2001;48:629–36). 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 enteric 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 treatment of 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 acidophilus species 299 stabilises the gut mucosal barrier in patients with ulcerative colitis and in the interleukin 10 knockout mouse model of colitis.3,4 There was also a reduction in laboratory markers and indices of disease activity in ulcerative colitis patients.5 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
J S KIRK
K R GARDINER
Department of Surgery, Queen’s University of Belfast, Belfast, UK.


Probiotics in Crohn’s disease

EDITOR,—In their “therapy updates”, Professors Shanahan (Gut 2001;48:609) and Professor Colombel et al (ibid 2000;48:629) 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 “probiotics 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 on ulcerative colitis and poushitis.

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 tried 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). One of our previously unpublished observations seems 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 stratified according to pathological 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 boulardii* 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 Olgetta 60, 20132 Milan, Italy

guslandi.marino@irs.it

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**Table 1** Results of questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Informed consent is an integral part of good medical practice.</td>
<td>13 (76%)</td>
<td>4 (24%)</td>
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<td>Consent forms are readily available</td>
<td>16 (94%)</td>
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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. 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. 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.

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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-MMP) 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-MMP 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 and its methylated metabolites detected. 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 has a shelf life of almost three months. 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. The dosage of the drug will be 6-TG (Lanvis, Thioguanine Tabloid in the USA) in a starting dose of 40 mg orally per day.

The aim of the study is to obtain a clearer understanding of adverse events in conjunction with 6-TG serum levels in IBD, especially in patients with a history of skin rashses, 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 Welcome is no longer interested as the drug is out of patent, similar to the situation with bethamethasone for IBD in the past.
Liver Biopsy Evaluation. Histological features of diseases included in the biliary cirrhosis, primary sclerosing cholangitis, Hodgkin's lymphoma, primary 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 comprehensive lists it provides of possible causes of the main patterns of damage identified. A large number of illustrations, mostly coloured, of good quality, are also included. Using this approach should enable the pathologist assessing a liver biopsy specimen to suggest a number of likely diagnoses. Dependent on clinical information provided either at the time of biopsy or subsequently, it should be possible to make a specific diagnosis in most cases. For some of the morphological landmarks identified, the lists of possible causes are so long that their practical value is limited—for example, some 80 causes of “lobular necrosis with inflammation” are listed. The experienced liver pathologist would soon recognise that many of the examples listed are not relevant to the case being assessed but this may not be so easy for the less experienced person. There are also a number of instances where conditions are inappropriately included as possible causes for a particular pattern of damage—for example, right sided heart failure and veno-occlusive disease are listed as causes of portal fibrosis whereas these are both more typically associated with parenchymal fibrosis. There are also a few occasions on which one might quibble with the terminology used—for example, the term “piecemeal necrosis” is used rather than the more preferred “interface hepatitis”, “autoimmune hepatitis” rather than “dysplastic nodule”, and autoimmune cholangitis is regarded as a variant of autoimmune hepatitis whereas most people now consider this to be a form of AMA negative primary biliary cirrhosis.

For pathologists with little experience of looking at liver biopsies, this book should serve as a useful practical introduction to liver biopsy interpretation. 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 text covering upper gastrointestinal surgery other than HPB but also including the small intestine which is a frequently forgotten part of the gastrointestinal tract coming as it does between the colorectal and upper gastro-intestinal 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 up to date nature of chapters varies with the bibliography, in some cases being up to the late 1990s but in others being really the early 1990s. This 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 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 produce 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 diseases with 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
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: 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 3 517 5150; fax: +972 3 517 5155; email: gi@targetconf.com
Survey of informed consent for endoscopy

A I THURAISINGAM

Gut 2001 49: 874
doi: 10.1136/gut.49.6.874

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