Aminosalicylate as prophylaxis for Crohn's disease

Editor,—We read with interest the recent clinical alert commentary by Rutgeertens (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). The 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 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% v 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 at al is also worthy of comment. A total of 131 of 318 randomised patients were protocol violators. Meta-analysis of previous randomised controlled trials concerns 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.

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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 the gut microflora remains limited. However, the increasing data showing a reduction in inflammation and symptoms in experimental and clinical enteroctitis 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 plantarum 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 patients with 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.

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Probiotics in Crohn's disease

Editor,—In their “therapy updates”, Professor Shanahan (Gut 2001;48:609) and Professor Colombel et al respectively addressed the issues of “probiotics in IBD” and of “antibiotics in Crohn’s disease”. We 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 in ulcerative colitis and pouchitis.

As both authors omitted to mention it, I feel obliged to quote our own study with Saccharomyces bouardii, 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 bouardii, 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). Our preliminary unpublished observations seem to suggest that a lower dose may be equally effective, provided that Saccharomyces bouardii is taken every day. Clearly, additional studies are needed before advising the use of Saccharomyces bouardii or other probiotics in the long term management of Crohn’s disease. As Colombel et al reminded us, patients should be stratified accordingly 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.

Table 1 Results of questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Yr</th>
<th>No</th>
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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 attending 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 endoscopy?</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>Finalised and same system of obtaining consent available for inpatients as outpatients?</td>
<td>12 (71%)</td>
<td>5 (29%)</td>
</tr>
</tbody>
</table>

ask about current practice in the unit with regard to consent for outpatient endoscopy. An accompanying letter explained the rationale for the questionnaire. Both district general and teaching hospitals were included. Seventeen of 20 units (85%) responded and each of the questionnaires returned was fully completed. Table 1 shows the results.

Although this simple questionnaire survey only examined one postgraduate region and did not cover a large number of units, there was a high response rate and so the results are representative of current practice within this region and probably reflect practice in 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 busy working environment, extra time spent explaining procedures may not appear productive but in the longer term will safeguard against complaints and even litigation.

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-methylthioguanine (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 were maintained on unmethylated metabolites detected. 4 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. 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 mediation will be 6-TG (Lanvis, Thiogaunine 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 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 it seems to be interested as the drug is out of patent, similar to the situation with beclomethasone for IBD in the past. 5

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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 C infection, 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 changes involving the main components of the liver. The person assessing a liver biopsy specimen is then invited to identify a number of main "morphological landmarks" in the specimen (for example, portal hepatitis with plasma cells and bile duct paucity), for which tables listing possible causes are provided. Having thus identified a number of possible diagnoses (e.g. alcoholic liver disease, autoimmunity, cholangitis, Hodgkin's lymphoma, primary biliary cirrhosis, primary sclerosing cholangitis, and viral hepatitis type C) are all listed as possible causes of the two features listed above, the reader is referred to brief summaries of the main histological and clinical features of diseases included in the differential diagnosis, in the hope that a definite diagnosis can be made.

The main strength of this book lies in the comprehensive lists it provides of possible causes of the main patterns of damage identified. A large number of illustrations, mostly colour, of high 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," among other things.

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 HUBISCHER


This is a new comprehensive text covering upper gastrointestinal surgery other than HPB but all listed in the 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 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. 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 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 are more up to date and focus on controversial issues such as investigation and management of cancer, pillation 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

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 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

**14th Intensive European Course of Digestive Endoscopy**

This course will be held on 17–18 December 2001 in Strasbourg, 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

**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