

# PostScript

## LETTERS

### A shake of the head to a wink of the anus

We read the case report of Malouf and Kamm (*Gut* 2001;48:728-9) with interest. However, we disagree with some of the science and suggest an alternative explanation for their findings.

Firstly, there is much data to suggest that sympathetic innervation of the internal anal sphincter is in fact excitatory. The paper that they cite<sup>1</sup> (from their own institution) showed that noradrenaline, the principal postganglionic neurotransmitter of the sympathetic nervous system, caused contraction of this tissue in vitro. Operative in vivo studies of presacral nerve stimulation have indeed been contradictory, showing both an increase<sup>2</sup> and decrease<sup>3</sup> in internal anal sphincter tone; this probably reflects little more than differences in stimulation parameters. However, sympathetic blockade effected either by infusion of the  $\alpha$  adrenoceptor antagonist phentolamine<sup>4</sup> or by high spinal anaesthesia<sup>5</sup> produces a significant fall in internal anal sphincter tone. This is evidence of tonic, excitatory, sympathetic innervation of the internal anal sphincter, not of "extrinsic sympathetic drive which relaxes the sphincter", as described by Malouf and Kamm.

Secondly, acetylcholine relaxes internal anal sphincter in vitro,<sup>6</sup> an action blocked both by atropine and nitric oxide synthase inhibitors. This implies that acetylcholine, the principal postganglionic neurotransmitter of the parasympathetic nervous system, is inhibitory and acts via muscarinic receptors and its effects are mediated by nitric oxide. Low spinal anaesthesia has little effect on anal canal resting pressure, suggesting that there is negligible tonic parasympathetic discharge to the internal anal sphincter.<sup>7</sup> We are not aware of any convincing data that enable Malouf and Kamm to make the unreferenced statement that there is "normal extrinsic parasympathetic excitatory [sic] drive to the internal anal sphincter".

Finally, the anal canal normally remains closed at rest because of the tone of the internal anal sphincter, which contributes around 80% of resting anal pressure.<sup>8</sup> Most of this contraction is attributable to intrinsic myogenic tone although there is some tonic sympathetic discharge, as outlined above. Malouf and

Kamm describe the anus of a spinal cord injured patient as having "gaped after digital examination for several minutes" and state that this might reflect loss of "normal extrinsic parasympathetic excitatory [sic] drive to the internal anal sphincter". A much simpler, and pharmacologically correct, explanation would be that digital examination of this patient evoked the rectoanal inhibitory reflex and induced internal sphincter relaxation. Indeed, we would dispute that normally "the anal canal remains closed before, during, and after examination". When the fingertip passes into the rectum of a non-spinal injury patient, a definite relaxation of the internal anal sphincter is often felt. This is not normally sustained for minutes, and it is this abnormality that is interesting in the case they report. High resting pressures are often seen in spinally injured patients and many of them use digital rectal stimulation to aid defecation.<sup>8</sup>

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### Author's reply

I am grateful to Drs Jones, Brading, and Mortensen for their comments. I agree that the extrinsic sympathetic innervation to the internal sphincter is predominantly excitatory, and that the parasympathetic extrinsic innervation causes internal sphincter relaxation. As mentioned in their letter, our own in

vitro studies have demonstrated this convincingly. That we stated the reverse in our "Gut file" case report was a simple error, and I appreciate the correction.

The main point of the report however remains the original description that gaping of the anal canal, with failure to return to its state of normal resting tone, after simple examination may reflect underlying extrinsic neurological damage. Although it is true that approximately 80% of the resting anal tone is contributed to by intrinsic myogenic activity of the internal sphincter in health, we do not know how loss of the normal extrinsic nerve supply may alter smooth muscle function. Damage to the extrinsic nerve supply affecting the sympathetic or parasympathetic components may also result in altered sphincter control and behaviour.

I doubt that the rectoanal reflex was the cause of this patient's sustained anal relaxation. In healthy subjects this reflex requires rectal distension, which does not occur during simple digital examination. Furthermore, any slight relaxation that might occur during digital examination is normally short lived and ceases when the finger is withdrawn. As stated in their letter, we believe it is this failure of the sphincter to return to a closed state that may be a pointer to underlying neurological disease.

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### Calpain inhibitor I and colonic inflammation induced by DNBS in the rat

We read with interest the paper by Cuzzocrea *et al* in which they demonstrated the marked beneficial effects of calpain inhibitor I on colonic inflammation induced by dinitrobenzene sulphonic acid (DNBS) in the rat. On the basis of their findings, they suggest that calpain inhibitor I treatment may be useful in inflammatory bowel disease (*Gut* 2001;48:478-88).

It is debatable whether a model that is associated with a mortality of 40% and 80% at two and six days, respectively, after induction of colitis has any relevance to human disease. The different numbers given in the text (seven animals per group) and figure 4 (10 rats in each group) further confuse interpretation of the mortality data. The authors have apparently taken their methods for induction of colitis from previously published work although the paper that they quote described induction of *ileitis* (not colitis) in guinea pigs.<sup>1</sup> We also use a rat model of colitis and would suggest that intrarectal administration of 20 mg trinitrobenzene sulphonic acid in 40% ethanol is associated with a mortality of less than 8% at seven days.

In a separate experiment, the authors assessed the effect of calpain I inhibitor on the histological severity of colitis, weight loss, and expression of adhesion molecules in the colon. It is not clear from either the methods or the results as to how many animals were in each group. In the text the authors state that seven animals were in the sham group. However, in figures 1, 3, 5, 6, and 9, values are given for the mean of 10 rats in each group. The numbers of animals in the colitis group is not

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given in the text but the figures states 10 rats/group. Was this 10 rats at four days after induction of colitis or 10 rats at the beginning of the experiment (day 0)? If 10 rats remained at four days, what was the starting number; presumably many more with a predicted mortality of about 60%?

### A Ballinger O Azooz

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### Reference

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### Authors' reply

We very much appreciate the interest of Drs Ballinger and Azooz in our work.

In 1997, we discovered that calpain inhibitor I exerted potent anti-inflammatory effects in rats with endotoxin shock.<sup>1</sup> We therefore speculated that calpain inhibitor I may reduce the degree of inflammation and tissue injury associated with other models of inflammation, including colitis. The model of hapten induced colitis used by us is similar, but not identical, to the one introduced by John Wallace and colleagues in 1989 (*Gut* 2001;48:478–8) in which instillation of a solution containing a "barrier breaker" (0.25 ml of 50% ethanol) and the hapten 2,4,6-trinitrobenzene sulphonic acid (TNBS 5–30 mg) are used to cause colonic ulceration and inflammation in the rat. Clearly, the severity of colitis caused and the mortality of any given model may vary with the experimental design used. We would like to propose that the high mortality associated with our model of hapten induced colitis is a reflection of the fact that our animals were exposed to the hapten for a relatively long period. As stated in the methods section of our article, adult male Wistar rats were anaesthetised with isoflurane and received intrarectal administration of 25 mg of dinitrobenzene sulphonic acid (DNBS) for a period of 15 minutes.<sup>2</sup> Exposure of the colon of the mouse to 1 mg of TNBS even for very short periods (30 seconds) also results in a substantial degree of mortality<sup>3</sup> but mortality may vary between studies even if the same experimental protocol is used by the same investigator.<sup>4</sup> When investigating the effects of insulin-like growth factor 1 on the linear growth retardation associated with colitis,<sup>5</sup> Ballinger *et al* exposed prepubertal rats (26 days old, anaesthetised with Hypnorm) of both sexes to 8 mg of TNBS in 40% ethanol for an unspecified period of time. When investigating the role of neuropeptide Y on the weight loss associated with experimental colitis, investigators from this group used intrarectal administration of 20 mg of TNBS (for an unspecified period of time) to cause colitis in male Wistar rats.<sup>6</sup> Unfortunately, neither study provides any histological evidence of the severity of the colitis or any mortality data.<sup>5,6</sup> We understand from Dr Ballinger that the mortality of 8% cited in her letter is a summary of experiments carried out by her group over the last 4–5 years. These mortality values have not been published.

We apologise if the number of animals studied was less clear than we thought. All of the data outlined in figures 1, 3, 5, 6, and 9 were, indeed, based on results obtained from 10 animals (survivors). The n numbers of the

individual groups at the beginning of the experiments were the following: sham operated treated with vehicle, n=10; sham operated animals treated with calpain inhibitor I, n=10; DNBS control, n=18; DNBS rats treated with calpain inhibitor I, n=13.

In the final paragraph of our article (*Gut* 2001;48:478–88), we stated that our findings suggest that calpain inhibitor I may be useful in conditions associated with local or systemic inflammation, including inflammatory bowel disease. In the last few months, we have reported that calpain inhibitor I also attenuates the multiple organ injury and dysfunction associated with haemorrhagic shock<sup>7</sup> as well as the tissue injury associated with pleuritis (induced with carrageenan) and arthritis (induced by collagen).<sup>8</sup> All of these findings support the view<sup>1</sup> that calpain inhibitor I exerts potent anti-inflammatory effects *in vivo*.

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### Mucosal barrier function and the commensal flora

We read with interest the article by Garcia-Lafuente *et al* (*Gut* 2001;48:503–7). Their results demonstrate that strains of endemic gut bacteria can affect gut mucosal barrier function, as measured by intestinal permeability, and that the effect may be potentially beneficial or harmful depending on the specific bacterial strains administered.

These findings help to explain and corroborate the interesting findings that have been

emerging from clinical and experimental studies investigating the use of probiotics in inflammatory bowel disease (IBD). It is known that development of colonic inflammation in genetic models of IBD is dependent on the presence of intestinal bacteria. In human studies, an imbalance in colonic bacteria has been described in patients with IBD with a reduction in potentially protective organisms such as bifidobacteria and lactobacilli and an increase in *Escherichia coli*. Furthermore, treatment with probiotics such as lactobacilli has been shown to reduce intestinal inflammation and inflammatory response in experimental models of colitis and to reduce symptoms and inflammatory scores in patients with IBD.

We have recently investigated the effect of *Lactobacillus plantarum* species 299 on the gut mucosal barrier both in patients with ulcerative colitis and in the interleukin 10 knockout mouse model of colitis.<sup>1,2</sup> This probiotic was found to improve gut mucosal barrier function in the mouse model, as measured by a reduction in gut permeability and a reduction in the concentration of circulating antibody to endotoxin. These changes correlated positively with a reduction in colonic inflammation. In a study of patients with ulcerative colitis, *Lactobacillus plantarum* probiotic therapy was also found to improve gut mucosal barrier function, as measured by a reduction in the circulating antibody to endotoxin.<sup>2</sup> The findings of our studies and those of Garcia-Lafuente *et al* suggest that probiotics such as *Lactobacillus plantarum* are capable of improving gut mucosal barrier function in both normal and inflamed bowel. It is possible that this probiotic induced enhancement of the gut barrier may be a mechanism by which probiotics are effective in reducing intestinal inflammation in experimental models of colitis and IBD.

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### References

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### Authors' reply

We value the comments made by Mr Kennedy *et al* and are grateful to them for bringing to our attention their report to the Surgical Research Society on the effect of *Lactobacillus plantarum* species 299 on the gut mucosal barrier in the interleukin 10 knockout model of colitis. While we agree with their points regarding the usefulness of some probiotic strains for the prevention of gut barrier dysfunction associated with mucosal inflammatory conditions, we also would like to stress the fact that bacteria may also influence colonic barrier function in a normal setting. In our experimental model, we were able to detect changes in the colonic permeability to a small molecular size probe induced by commensal bacteria, without any significant effect on the lumen to blood passage of a large molecular size probe—that is, excluding changes due to epithelial cell damage. This

finding suggests that in a physiological state, colonic permeability can be influenced by the quality of the flora colonising the mucosal surfaces. Further studies are needed for a better understanding of the interplay between resident bacteria and the host at the mucosal interface.

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## BOOK REVIEWS

### How to Read a Paper

T Greenhalgh. London: BMJ Publishing Group, 2001, £16.95, illustrated, pp 222. ISBN 0 7279 1578 9

I suppose people still read scientific papers, or so editors of scientific journals and their publishers would like to believe, and this is the assumption implicit in the title of this excellent book. On the other hand, the abundance of reviews, summaries, and refresher courses sometimes makes me wonder who actually reads them. Apart from researchers active in their particular corner of the field and referees engaged in peer review, most people, I fancy, only read the abstract.

When a while ago I was appointed to the editorship of *Gut*, I had my introductory meeting with Stephen Lock, the then editor of the *BMJ* and editor in chief of all of the BMA journals. George, he said, there is nothing so ephemeral as a scientific paper. The feeling of disbelief, surprise, and shock I felt then is still clear in my memory but of course he was right. How many of us consult even the really great past papers in gastroenterology—for example, Sir James Black *et al*'s "Definition and antagonism of histamine H<sub>2</sub> histamine receptors" (*Nature* 1972;236:385). One generally gets the feeling that most of us find it very difficult to cope with the current volume of scientific research that thuds on one's desk every month, or appears on our screens.

The drive to publish is well documented and generated by genuine discovery, by career and funding pressures, or by marketing needs. Publication of research in hepatology and gastroenterology has been balkanised between some 80 journals. However, more does not necessarily mean better and this is where Trisha Greenhalgh's book comes in. It really contains what it says on the cover, namely the basis of evidence based medicine. This is the second edition, the first having appeared in 1997. The text has been brought up to date and deals with current shibboleths, such as guidelines, for example. The chapter on papers that report drug trials is very valuable and gives sound and irreverent advice on how to deal with drug reps and drug advertising, especially important at present when more and more research seems to be controlled by the pharmaceutical giants. The book has been highly successful, and has been translated into six languages. Dr Greenhalgh writes very well and what might have been a rather dry text is enlivened and made enjoyable by her informal and iconoclastic style, and by practical examples.

Every aspect of clinical scientific presentation is covered and there are numerous and

very helpful checklists and appendices. If, like me, you are a self taught Medline hacker, the book is worth buying just for the chapter on searching the literature. A self confessed innumerate person, Dr Greenhalgh has written one of the clearest and non-frightening chapters on medical statistics I have come across. Actually, I think that the author has been too modest in her title because her book contains not only comprehensive advice on how to read a paper but readers will acquire sound and essential guidance on how to plan research and how to write it up. Those embarking on a medical career will find it invaluable but so will seasoned practitioners in any speciality.

It is a cliché of reviewing to say that "everyone should have a copy of this book" but it happens to be true in this instance. At £16.95 it is eminently affordable and a sound investment. Even editors should own it, and my copy will sit on my editorial desk from now on.

**G Misiewicz**

### Diseases of the Gastroesophageal Mucosa. The Acid-Related Disorders

Edited by J W Freston. New Jersey: Humana Press, 2001, \$99.50, pp 200. ISBN 0 986 03965

This appears to be the first volume of a planned series entitled *Clinical Gastroenterology*, intended mainly for clinically orientated gastroenterologists aiming to keep their noses ahead of the field without going into full training. The editor is James Freston and those who have been involved with him in workshops and symposia will not be surprised by the precision and clarity he has drawn from his authors. This is an important feature because despite being a relatively small volume of approximately 70 000 words, it manages to comprehensively cover all aspects of peptic ulcer disease, functional and undiagnosed dyspepsia, and gastro-oesophageal reflux.

The 18 contributors are established experts based in the USA. With the promotion of managed health care in that country it is unsurprising that their discussions encompass not only the clinical but also the cost effectiveness of diagnostic and therapeutic policies. Each chapter is fully referenced, not only from the usual gastroenterology journals, but also from texts unlikely to be on the reading list of the average UK practitioner.

The chapters covering gastro-oesophageal reflux disease (GORD) emphasise the multifactorial nature of the disease and include an evidence based review of the role of lifestyle factors and an analysis of step-up versus step-down therapy. Barrett's oesophagus, an area of continuing confusion, is dealt with succinctly. Nevertheless, sufficient evidence is quoted to tempt even the most sceptical reader to at least consider the possible benefits of surveillance programmes.

Although most UK gastroenterologists accept that non-cardiac chest pain is often of oesophageal origin, they would be less certain about the role of GORD in laryngeal symptoms, asthma, or chronic cough. Pandolfino and Kahrilas provide persuasive evidence to support these concepts but there will be general relief that a three month therapeutic trial of a proton pump inhibitor is the favoured initial approach to management, and that pH and manometric studies should be reserved for resistant cases or prior to referral for fundoplication.

Management protocols are increasingly demanded and those looking for a resource to devise acute non-variceal bleeding guidelines will welcome Machicado and Jensen's chapter. The clinical, laboratory, and endoscopic risk factors for rebleeding and death are delineated and selection criteria for endoscopic intervention are substantiated.

The retention of the confusing term "non-ulcer dyspepsia" rather than "functional dyspepsia" is a minor irritation. Nevertheless, the chapter covering this nebulous topic appropriately reviews current opinion and concludes that *Helicobacter pylori* and gastric acid have little to do with endoscopically negative belly ache.

For those who, like your reviewer, need to update their lectures, this book will be an invaluable aid. If subsequent volumes are of comparable quality the series deserves to find a place on the shelves of UK gastroenterology departments, although the price of \$99 for a 200 page volume may discourage its purchase.

**M Lancaster-Smith**  
In addition to the above, Blanca

## NOTICES

### Broad Medical Research Program—Inflammatory Bowel Disease Grants

Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US\$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no submission deadline), simple application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

### 9th Symposium on Neurogastroenterology & GI Motility

This will be held on 22–24 March 2002 in Iowa, USA. Further information: Louis G Crist, Director of Continuing Medical Education, University of Iowa College of Medicine, 300 Medicine Administration Building, Iowa City, IA 52242-1101, USA. Tel: +1 319 335 8599; email: louis-crist@uiowa.edu

### European Association for the Study of the Liver: 37th Annual Meeting

The EASL Annual Meeting will be held on 18–21 April 2002 in Madrid, Spain. Further information: EASL Liaison Bureau, c/o Kenes International, 17, rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 04 88; fax: +41 22 732 28 50; email: info@easl.ch; website: www.easl.ch