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 (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 contradic-

tory, showing both an increase and decrease in internal anal sphincter tone; this probably reflects little more than differences in stimulation parameters. However, sympathetic blockade effected either by infusion of the α adrenoreceptor antagonist phentolamine or by high spinal anaesthesia 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, 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. We are not aware of any convincing data that enable Malouf and Kamm to make the unrefereed statement that there is “normal extrinsic parasympathetic excitatory [sic] drive to the internal anal sphincter”. A much simpler, alternative 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 in fact excitatory. The paper that they cite (from their own institution) showed that intrarectal administration of 20 mg trinitrobenzene sulphonic acid in 40% ethanol is associated with a mortality of less than 8% at seven days. We also use a rat model of colitis and would suggest that intrarectal examination of this patient (not colitis) may have caused anal gape. A shake of the head to a wink of the anus.

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, alternative 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 in fact excitatory. The paper that they cite (from their own institution) showed that intrarectal administration of 20 mg trinitrobenzene sulphonic acid in 40% ethanol is associated with a mortality of less than 8% at seven days. 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 inhibitor I 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 visible.

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given in the text but the figures state 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**  
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**Authors’ reply**  
We very much appreciate the interest of Drs Ballinger and Azzo in our work.  

In 1997, we discovered that calpain inhibitor I exerted potent anti-inflammatory effects in rats with endotoxin shock.1 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 1989; 30:478–87) 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, 25 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 conditions 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 intracolonic administration of 25 mg of dinitrobenzene sulphonic acid (DNBS) for a period of 15 minutes.1 Exposure of a solution of the mouse to 1 mg of TNBS even for very short periods (30 seconds) also results in a substantial degree of mortality but mortality may vary between studies even if the same experimental protocol is used by the same investigator.2 When investigating the effects of insulin-like growth factor 1 on the linear growth retardation associated with colitis, Ballinger et al exposed prepuberal 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 intracolonic administration of 20 mg of TNBS (for an unspecified period of time) to cause colitis in male Wistar rats.3 Unfortunately, neither study provides any histological evidence of the severity of the colitis or any mortality data.1,2 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 as well as the tissue injury and reduce symptoms with pleuritis (induced with carrageenan) and arthritis (induced by collagen).4 All of these findings support the view1 that calpain inhibitor I exerts potent anti-inflammatory effects in vivo.  

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**References**  

**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 function 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 permeability to a small molecular size probe induced by commensal bacteria, without any significant effect on the luminal to blood passage of a large molecular size probe—that is, excluding changes due to epithelial cell damage. This is
How to Read a Paper

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 an 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 with me. 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 and so will seasoned practitioners in any specialty.

It is a cliché of reviewing to say that “every-one 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 Mu cosa. The Acid-Related Disorders

This appears to be the first volume of a planned series entitled Clinical Gastroenterology, intended mainly for clinically oriented 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 gastrooesophageal 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 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 gastrointestinal journals, but also from sources it is 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 sound 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 bellies.

For those who, like your reviewer, need to update their lectures, this book will be invaluable. 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