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 contradictory, 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-adrenoceptor 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 modulated 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 excitation [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-sphincter injured patient, a definite rectoanal inhibitory reflex is induced, which relaxes the internal anal sphincter 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 spinaled patients and many of them use digital rectal stimulation to aid defecation.

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References

Author’s reply
I am grateful to Drs Jones, Bradling, 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 anal incoordinate peristalsis. 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 Cuzzoeca 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 colitis in guinea pigs. 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
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%?

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References


Authors’ reply

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

In 1997, we discovered that calpain inhibitor I exerted potent anti-inflammatory effects in rats with endotoxin shock.1 We subsequently 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;34:478–87) 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 50 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 manipulations 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.1 Exposure of the colon of the mouse to 1 mg of TNBS even for very short periods (30 seconds) results also 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 I on the linear growth retardation associated with colitis,3 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 intrarectal administration of 20 mg of TNBS for an unspecified period of time to cause colitis in male Wistar rats.4 Unfortunately, neither study provides any histological evidence of the severity of the colitis or any mortality data.5 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;48:478–87), we stated that our findings suggest that calpain inhibitor I may be useful in conditions associated with local or systemic inflammation, including the development of colonising endotoxin 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 induced with pleuritis (induced with carrageenan) and arthritis (induced by collagen).4 All of these findings support the view that calpain inhibitor I exerts potent anti-inflammatory effects in vivo.

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References


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 improvement in experimental 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.6 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 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.7 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 intestinal mucosal barrier mechanism by which probiotics are effective in reducing intestinal inflammation in experimental models of colitis and IBD.

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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 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 gut 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
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 editorialship 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. How many of us consult even the really 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.

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