VISCERAL PERCEPTION

Sensation and gas dynamics in functional gastrointestinal disorders

J-R Malagelada

Gut 2002;**51**(Suppl I):i72–i75

Our current knowledge of motor and sensory functions in the human gut is critically reviewed, showing how the two may interact to produce symptoms in patients with functional gastrointestinal disorders. A local stimulus is necessary to activate the pathogenetic symptom generation process, and in many patients abnormal pooling of gas at various or extensive sites in the bowel and focal gut distension may provide the local stimulus, compounded by spatial summation phenomena and conscious visceral hypersensitivity. The interplay of these mechanisms results in the clinical expression of symptoms.

SUMMARY

Our current knowledge of motor and sensory functions in the human gut is critically reviewed, showing how the two may interact to produce symptoms in patients with functional gastrointestinal disorders. Published evidence of pathophysiological disturbances in patients with various functional conditions is analysed, and the possible role of local stimuli, particularly gas, is discussed. Recently developed methodology has enabled a fairly precise quantification of intestinal gas dynamics to be undertaken in healthy subjects and in patients with irritable bowel syndrome (IBS) and functional bloating. The results of these studies strongly suggest that inappropriate gas pooling and focal gut distension may provide a local stimulus, which is compounded by spatial summation phenomena and conscious visceral hypersensitivity. The interplay of these mechanisms results in the clinical expression of symptoms.

INTRODUCTION

Over the last two decades, sensory responses elicited by various intraluminal chemical and physical stimuli, together with local and extraintestinal modulating factors (neural, hormonal, and pharmacological), have been the subject of considerable clinical research. It is now apparent that intraluminal stimuli have the potential to trigger both conscious and non-conscious afferent activity. In humans, a single stimulus, depending on its intensity and location, has the potential to activate different nerve fibres, circuits, and unperceived viscero-visceral reflexes, all of which may result in a consciously perceived response.[1 2]

Conscious perception of focal gastrointestinal distension in humans is a widespread physiological phenomenon occurring from the oesophagus to the rectum. Stimuli such as transmucosal electrical discharge are though to bypass the mechanoreceptors and activate nerve terminals directly.[3] In some parts of the gastrointestinal tract, such as the stomach, temperature variations may also induce conscious perception.[4 5] Many, if not all, of these physical stimuli have the potential to trigger consciously perceived responses that may or may not incorporate a change in motor activity. These observations provide indirect evidence to show that viscero-visceral motor reflexes are actively involved in the regulation of gastrointestinal motor function.

It is of interest that chemical stimuli, such as intraluminal fat, do not always induce a significant degree of conscious perception by themselves, although they do appear to critically alter the threshold for perception to distending stimuli (fig 1).[6] For these reasons, postprandial perception of gastrointestinal events may be different to that seen in fasted subjects.

In addition to nutrients, various other key modifiers of gastrointestinal perception have been identified. Some operate within the gut itself and others at various levels within the neurohormonal control hierarchy, which extends from the brain to the gastrointestinal tract.

Firstly, and rather critically to the discussion that follows, simultaneous conditioning stimuli appear to play an important role in sensitivity. Repeat focal distension of a gut segment either sensitises or desensitises the segment to further distension,[7 8] supporting the concept that under certain circumstances hypersensitivity may be induced by repeated focal stimuli. It is even more important to recognise that a phenomenon of spatial summation operates in the human gastrointestinal tract (fig 2). This means that when focal distension is produced simultaneously at various sites, even at sites distant from one another, there is a marked increase in perception which is disproportionate to that induced by distension of a single intestinal site.[9 10] Spatial summation phenomena probably play a very important role in certain pathological conditions, for instance by excess or trapped intestinal gas, in which there is multiple point stimulation of the gastrointestinal tract.

Extraintestinal modulatory factors also play a role in visceral perception. We have shown for example that activation of sympathetic tone, produced by inducing abrupt venous blood pooling in

Correspondence to:
Professor J Malagelada, Hospital Universitari Vall d'Hebron, Autonomous University of Barcelona, 08035 Barcelona, Spain;
jrmalagelada@terra.es

Abbreviations: CNS, central nervous system; IBS, irritable bowel syndrome.

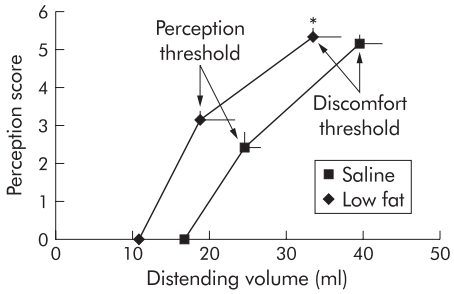

Figure 1 Perception of intestinal distension: effect of fat infusion (0.5 kcal/min). *p<0.05 versus saline control. Reproduced from Accarino and colleagues.[6]

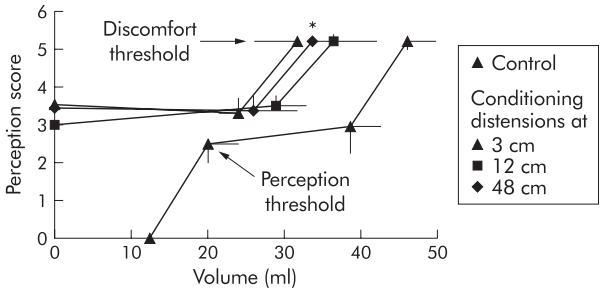

Figure 2 Effect of simultaneous conditioning on perception of intestinal distension. Values are mean (SEM). *p<0.05 versus control. Reproduced from Ness and Gebhart.[8]

the legs, increases perception of gastrointestinal distension.[11] The subjects' attention levels or their distractibility has been shown to substantially alter the magnitude of perception of a focal distending stimulus, as well as the level of perception over the abdominal reference area as a whole.[12] Important somatic-visceral interactions are also thought to play a role in visceral perception, as stimulation of somatic dermatomes via transcutaneous electrical impulses has been shown to modify perception of visceral stimulation independently of changes in attention levels.[13]

THE FUNCTIONAL PATIENT AND THEIR PATHOPHYSIOLOGICAL FEATURES

The concept of the "functional patient" (that is, those with functional gastrointestinal disorders) is an idea of a disease rather than a specific clinical entity. The arguments supporting such contentions are compelling. Firstly, although functional patients have some readily identifiable common features (and experienced practitioners are good at identifying them almost at a glance) there are no two functional patients alike. Even if generous limits are set for different symptomatic expressions, there are still multiple subgroups and unclassifiable cases are seen frequently.[14] Symptomatic expression of these conditions is well established: pain, bloating, altered bowel habit, nausea, and/or borborygmi, but in reality patients present with almost limitless combinations of symptoms which makes it unlikely that examination of symptom clusters will contribute towards meaningful discrimination between different aetiologies—that is, mural inflammation, neuromuscular disorders, and centrally induced disturbances. This is probably true of the pathophysiological features, such as visceral hypersensitivity and/or contractile abnormalities also. Instead it is likely that the presenting symptoms and the sensorimotor abnormalities observed under laboratory conditions are in fact stereotyped expressions of a diverse range of gastrointestinal disorders, and as such they should not be regarded as reliable indicators of specific mechanistic disorders.

Secondly, serious consideration needs to be given to the mechanisms that underlie the transformation of a given condition with a specific aetiology into a secondary condition. For example, it is plausible, although by no means proven, that low grade residual inflammation and changes in enterochromaffin cells may be important disease mechanisms in the evolution of post-gastroenteritis IBS.[15 16] However, it is also known that individuals subjected to stress during or after gastroenteritis are more likely to develop chronic symptoms,[17] indicating that a verifiable morphological abnormality has the potential to be modulated or transformed by extraintestinal factors which in themselves are determinants of the clinical outcome.

Finally, there appears to be an overlap in presenting disorders between patients and healthy subjects. General population surveys consistently identify a substantial group of healthy subjects who, on questioning, acknowledge symptoms that are similar to those manifested clinically in patients but who do not consider themselves abnormal enough to warrant medical consultation. A concept of psychologically motivated consulters versus non-consulters has been developed to explain this phenomenon.[18] An alternative explanation for the non-consulters is that under certain circumstances factors such as excessive or inappropriate food ingestion, alcohol consumption, stress, or iatrogenic triggers combine in a way that overloads or sensitises the "alerting" neurosensory apparatus of the gastrointestinal threshold but these are perceived as essentially "normal" or "healthy" responses.[19] In contrast, consulters would be alarmed by these abdominal signals and request medical attention.

Patients with functional gastrointestinal disorders therefore comprise an elusive target population. It is possible that greater attention should be directed towards factors that provoke and amplify symptoms, and that less emphasis should be given in attempting to identify symptom patterns as meaningful indicators of the underlying pathogenesis.

ABNORMAL PERCEPTION IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS

Accepting the premise put forward in the preceding section, that we still do not know precisely how to define a "functional patient", it is clear that certain pathophysiological patterns tend to be more common than in healthy individuals or in those with "organic" disease. Visceral hypersensitivity is foremost among these abnormalities and abnormal motor function is second. While there is evidence that both types of abnormality coexist, and that they sometimes share common mechanisms, it is also likely that they may be modified independently of one another.

Hyperalgesia to focal distension is present throughout the gastrointestinal tract of patients with functional disorders. Sometimes it is region specific, in which case only the segment from which symptoms appear to originate is hypersensitive, but very often regional specificity is not apparent. In patients with IBS for example, distension of the jejunum causes hyperalgesia as much as colonic distension. This form of regional non-specificity has been postulated as evidence that hyperalgesia originates at a superstructural level in the central nervous system (CNS) rather than in the gastrointestinal tract wall.

Electrical stimulation of the gastrointestinal tract in patients with IBS elicits less conscious hypersensitivity than that produced by mechanical distension. However, electrical stimulation triggers the same spinal convergence effects as mechanical stimulation, and is associated with an identical increase in the area of abdominal referral of discomfort as that induced by local stimuli.[20] Recent advances in positron emission tomography scanning and functional magnetic resonance imaging have made it possible to visualise differences in cerebral activity between healthy subjects and patients with

functional gastrointestinal disorders. However, further work is necessary in this area to elucidate the precise cerebral mechanisms that are involved in these events.

As has often been the case with other pathological processes, responses to pharmacological agents have been helpful in elucidating some of the mechanisms responsible for functional gastrointestinal disorders.[21] Experimental data indicate that agents acting on kappa-opioid receptors, neurokinin receptors, and 5-HT_3 receptors are all capable of modifying visceral hypersensitivity. However, clinical proof of their effectiveness is still being sought. None the less, the effectiveness of low dose tricyclic antidepressants in relieving symptoms lends support to the importance of visceral afferent sensory pathways in these patients.[22 23]

Evidence of motor dysfunction has been harder to unearth but several convincing examples may be cited here. In patients with diffuse oesophageal spasm, the disturbances of contractile activity in the body of the oesophagus have been shown by manometry to coincide with the onset of chest pain although it is also true that some aberrant contractions may be totally unperceived. In dyspepsia, a substantial proportion of patients have slow gastric emptying and failure of accommodation, although the exact proportion varies between studies, possibly depending on inclusion criteria.

The small bowel also manifests abnormal contractile patterns, detectable by manometry. However, reports of this procedure often fail to differentiate between serious neuromuscular disease (that is, pseudo-obstruction) and functional disorders. However, recent evidence showing that patients with IBS have diminished ability to propel a gas load infused into the upper small bowel supports the existence of a motor dysfunction in this disorder.[24]

An intriguing observation from many motility studies is that abnormalities are not detected in all patients, even when individual study cohorts are selected on the basis of common symptomatology. In contrast, similar types of motor abnormalities are sometimes observed in asymptomatic subjects. This apparent inconsistency has led some authors to dismiss dysmotility as a putative link between dysmotility and symptoms. This may be a precipitous conclusion as, at least in some patients, motor disturbances may result from abnormal neuromuscular reflex regulation and the symptoms themselves are sensory in origin. Thus both motor abnormalities and visceral hypersensitivity may have a common neuropathic source. In other patients it may be motor abnormalities that induce secondary transit disturbances which in turn stimulate sensory receptors. A third possibility is that the ability of motor abnormalities to induce perceptible symptoms may depend on the degree of ongoing activity within superstructures along the brain-gut axis. Again, pharmacological intervention provides an added insight into the pathophysiological situation. The now withdrawn 5-HT_3 antagonist alosetron is known to be beneficial in some patients with symptoms of diarrhoea.[25] This is attributed to its ability to relax the right colon and also to its antisecretory and putative visceral hypoalgesic effects. Therapeutic benefit with alosetron is probably achieved by simultaneously modifying several different functions: motor activity, secretion fluxes, and afferent sensory activity. In contrast, antispasmodic agents relieve abdominal pain associated with functional bowel disorders, principally on the basis of their ability to counteract bowel contraction. These agents lack hypoalgesic action and fail to normalise propulsive activity. Consequently, they are of little overall clinical benefit, except as sporadic pain relievers.

Prokinetic agents, such as cisapride, are regarded as being more beneficial in the management of dyspepsia associated with delayed gastric emptying than in the treatment of patients who have predominantly sensory disturbances or poor gastric accommodation. The effect of 5-HT_4 partial agonists on the colon has been shown to be beneficial in the management of IBS with constipation. These agents may promote colonic propulsion of residue and gas, and thus minimise focal distension, which is the principle source of pain and bloating.

THE NATURE OF THE PAINFUL STIMULUS

The above review of pathophysiological processes strongly suggests that sensory and motor dysfunctions are both directly implicated in the onset of symptoms. There is also evidence of extraintestinal involvement from the CNS. The key issue to be addressed is what unleashes these abnormalities and actually triggers the painful events? In our opinion inappropriate pooling of intraluminal contents in the form of solids, liquids, and gas each play a role in this process.

Stimulus production by solids

Solids enter the small bowel in considerable amounts. Early studies quantifying changes in solid mass in the stomach after a mixed solid-liquid meal show that mass in the stomach accounted for by solids is only reduced by 20% during the postprandial phase.[26] The solids are liquefied but they remain largely as particulate matter suspended in the liquid component of the gastric contents. The pylorus allows particles of up to 1 mm in diameter (usually <0.5 mm) to pass into the duodenum during the postprandial phase of digestion. Data from transit studies show that these small solid particles traverse the small bowel at approximately the same speed as liquids.[27] The particles accumulate in the colon where they reside for prolonged periods of time. Thus it seems likely that solids, in the form of liquid suspension, move through the small bowel and may potentially distend it to perception threshold levels. Focal accumulation could also in theory cause temporary obstruction.

The role of solid accumulation is probably more important in the colon than in the small bowel. Levitt *et al* have shown that feeding of non-fermentable fibre supplements to healthy volunteers induces a "bloating" abdominal sensation accompanied by much flatulence.[28] In contrast, clinical observations suggest that severely constipated subjects who do not pass stools for prolonged periods of time pack solids in the colon without complaining of bloating or other abdominal discomfort.

Stimulus production by liquids

Pooling of liquids in the small bowel is a potential source of intestinal distension and discomfort, and is thought to be one of the major mechanisms of pain in acute or subacute intestinal obstruction. However, there is no evidence of altered small bowel transit of liquids in patients with functional gastrointestinal disorders. In fact, most measurements of small bowel transit using soluble markers such as lactulose are normal, albeit these measurements tend to be performed in a fasting rather than a postprandial state, which is when the symptoms tend to develop. Liquid is unlikely to play a major role in the colon except perhaps in patients with symptoms of diarrhoea.

Stimulus production by gas

Gas is the factor that in our opinion has the highest probability of being a trigger for intestinal distension and afferent sensory stimulation. There are two major sources of gas in the gut: swallowed air and gas produced by bacterial fermentation of colonic contents. A third component, CO_2, is generated by an acid-base reaction in the duodenum. This is rapidly diffused back into the circulation and exhaled. CO_2 is therefore unlikely to cause distending stimulation.

Air entering the small bowel by the orogastric route is rapidly propelled forward by the intestine. Studies in healthy volunteers show that following infusion of an N_2 predominant mixture of gases just beyond the ligament of Treitz (using a broad range of infusion rates), the gas rapidly moves forward through the bowel and is expelled through the anus at about the same rate as it enters the upper intestine.[29] Thus there is

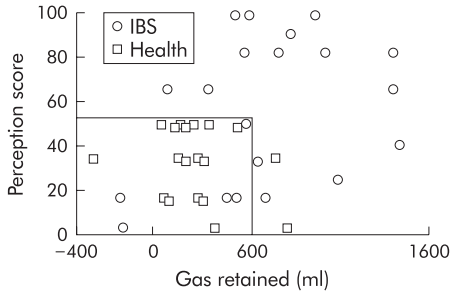

Figure 3 Intestinal gas dynamics and tolerance in healthy subjects and in patients with irritable bowel syndrome (IBS). Reproduced from Serra and colleagues.[24]

very little pooling of infused gas (usually <400 ml) in the small bowel and colon of normal subjects. Likewise, there is no detectable abdominal distension and no discomfort. Although healthy individuals are generally capable of very efficient gas disposal, there are a few who behave as "gas retainers" in that they are unable to expel the gas in an efficient manner and consequently become bloated and uncomfortable. This condition can be self induced by voluntary contraction of the anus in order to inhibit the spontaneous passage of gas.[30]

An abnormally high proportion of "gas retainers" are found among patients with IBS and functional bloating, and even those who do not retain abnormal quantities of infused gas often acknowledge significantly more abdominal discomfort that healthy individuals (fig 3).[24] These findings suggest that functional gastrointestinal disorders are a consequence of a mixed sensorimotor disorder which causes affected patients to exhibit both inefficient disposal of intestinal gas and abnormal tolerance to gas.

Impaired intestinal gas dynamics, and subsequent gas retention, implies that because motor activity is abnormal, gas is not propelled forward in a normal and efficient manner. Indeed, patients with IBS who retain gas abnormally continue to do so even with a rectal cannula. Coexisting visceral hypersensitivity amplifies the discomfort produced by abnormal gas retention and may even be responsible for abdominal symptoms occurring in patients in whom gas is retained below the normal threshold for discomfort.

The experimental evidence detailed above applies mostly to gas entering the gut proximally. However, I speculate that similar mechanisms would operate in the case of gas generated in the colon. In individuals who are able to expel the increased production of colonic gas efficiently, a flatulent state results. Those who do not expel the extra gas load generated by fermentation retain the gas and may develop symptoms, which are intensified by the phenomenon of visceral hyperalgesia.

Preliminary evidence suggests that the colon is more capable than the small bowel of accommodating gas without inducing discomfort. It is conceivable therefore that both motor and sensory abnormalities coexist in different proportions in individual patients. If gas retention affects different or extensive segments of the gut, the phenomenon of spatial summation further amplifies the discomfort, and may be a critical mechanism in many painful abdominal conditions.

The hypothetical pathophysiological model described above does not presuppose that the sensorimotor abnormality occurs either peripherally (in the gastrointestinal tract wall or adjacent neural structures) or in the CNS. Neither does it imply that relief of discomfort would necessarily require total correction of the sensory and motor abnormalities. Improvement in either could theoretically suffice to lower the threshold or the stimulus enough for symptoms to be ameliorated.

CONCLUSIONS

Abnormal regulation of motility and sensory function is at the root of symptom production in functional gastrointestinal disorders. A local stimulus is necessary to activate the pathogenetic symptom generation process, and in many patients abnormal pooling of gas at various or extensive sites in the bowel is the culprit which triggers symptoms. When patients complain of a gas problem, we ought to listen sympathetically, as they are probably right.

REFERENCES

1 **Cervero F**. Mechanisms of visceral pain: Last and Present. In: Gebhart GF, ed. *Visceral pain*. IASP Press, 1995:25–40.
2 **Wood JD**, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology: basic science. In: Drossman DA ed. *The functional gastrointestinal disorders*: Laurence KS: Allen Press Inc, 2000:31–90.
3 **Accarino AM**, Azpiroz F, Malagelada J-R. Symptomatic responses to stimulation of sensory pathways in the jejunum. *Am J Physiol* 1992;**263**:G673–7.
4 **Villanova N**, Azpiroz F, Malagelada J-R. Perception and gut reflexes induced by stimulation of gastrointestinal thermoreceptors in humans. *J Physiol* 1997;**502**:215–22.
5 **Villanova N**, Azpiroz F, Malagelada J-R. Gastrogastric reflexes regulating gastric tone and their relationship to perception. *Am J Physiol* 1997;**273**:464–9.
6 **Accarino AM**, Azpiroz F, Malagelada J-R. Modifications of small bowel mechanosensitivity by intestinal fat. *Gut* 2001;**48**:690–5.
7 **Serra J**, Azpiroz F, Malagelada J-R. Perception and reflex responses to intestinal distension in humans are modified by simultaneous or previous stimulation. *Gastroenterology* 1995;**109**:1742–9.
8 **Ness TJ**, Gebhart GF. Visceral pain: a review of experimental studies. *Pain* 1990;**41**:167–234.
9 **Serra J**, Azpiroz F, Malagelada J-R. Modulation of gut perception in humans by spatial summation phenomena. *J Physiol* 1998;**506**:579–87.
10 **Gracely RH**. Studies of pain in normal man. In: Wall PD, Melzac R, eds. *Textbook of pain*, 3rd edn. Edinburgh: Churchill Livingstone, 1994:315–36.
11 **Iovino P**, Azpiroz F, Domingo E, *et al*. The sympathetic nervous system modulates perception and reflex responses to gut distension in humans. *Gastroenterology* 1995;**108**:680–6.
12 **Accarino AM**, Azpiroz F, Malagelada J-R. Attention and distraction: effects on gut perception. *Gastroenterology* 1997;**113**:415–22.
13 **Coffin B**, Azpiroz F, Malagelada J-R. Somatic stimulation reduces perception of gut distension in humans. *Gastroenterology* 1994;**107**:1636–42.
14 **Talley NJ**, Boyce P, Jones M. Identification of distinct upper and lower gastrointestinal symptom groupings in an urban population. *Gut* 1998;**42**:690–5.
15 **Gwee KA**, Leong YL, Graham C, *et al*. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;**44**:400–6.
16 **Bose M**, Nickols C, Feakins R, *et al*. 5-Hydroxytryptamine and enterochromaffin cells in the irritable bowel syndrome. *Gastroenterology* 2000;**118**:A563.
17 **Neal KR**, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ* 1997;**314**:779–82.
18 **Drossman DA**, Creed FH, Olden KW, *et al*. Psychosocial aspects of functional gastrointestinal disorders. In: Drossman DA, ed. *The functional gastrointestinal disorders*. Laurence KS: Allen Press Inc, 2000:157–246.
19 **Notivol R**, Saperas E, Coffin B, *et al*. Gastric tone determines the sensitivity of the stomach to distension. *Gastroenterology* 1995;**108**:330–6.
20 **Accarino A**, Azpiroz F, Malagelada J-R. Selective dysfunction of mechanosensitive intestinal afferents in the irritable bowel syndrome. *Gastroenterology* 1995;**108**:636–43.
21 **De Ponti F**, Malagelada J-R. Functional gut disorders: from motility to sensitivity disorders. A review of current and investigational drugs for their management. *Aliment Pharmacol Ther* 1998;**80**:49–88.
22 **Clouse RE**. Antidepressants for functional gastrointestinal syndromes. *Dig Dis Sci* 1994;**39**:2352–63.
23 **Richeimer SH**, Bajwa ZH, Kahraman, *et al*. Utilization patterns of trycyclic antidepressants in a multidisciplinary pain clinic: a survey. *Clin J Pain* 1997;**13**:324–9.
24 **Serra J**, Azpiroz F, Malagelada J-R. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. *Gut* 2000;**48**:14–19.
25 **Camilleri M**, Mayer EA, Drossman DA, *et al*. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT_3 receptor antagonist. *Aliment Pharmacol Ther* 1999;**13**:1149–59.
26 **Malagelada J-R**. Quantification of gastric solid-liquid discrimination during digestion of ordinary meals. *Gastroenterology* 1977;**72**:1264–7.
27 **Carryer PW**, Brown ML, Malagelada J-R, *et al*. Quantification of the fate of dietary fiber in humans by a newly developed radiolabeled fiber marker. *Gastroenterology* 1982;**82**:1389–94.
28 **Levitt MD**, Furne J, Olsson S. The relation of passage of gas and abdominal bloating to colonic gas production. *Ann Intern Med* 1966;**124**:422–4.
29 **Serra J**, Azpiroz F, Malagelada J-R. Intestinal gas dynamics and tolerance in humans. *Gastroenterology* 1998;**115**:542–50.
30 **Serra J**, Azpiroz F, Malagelada J-R. Mechanisms of intestinal gas retention in humans: impaired propulsion versus obstructed evacuation. *Am J Physiol Gastrointest Liver Physiol* 2001;**281**:G138–43.