Digestive Diseases and Sciences, Vol. 40, No. 8 (August 1995), pp. 1607–1613

Heightened Visceral Sensation in Functional Gastrointestinal Disease Is Not Site-Specific

Evidence for a Generalized Disorder of Gut Sensitivity

K.C. TRIMBLE MD, R. FAROUK, FRCS, A. PRYDE, HNC, S. DOUGLAS, BSc, and R.C. HEADING, MD

Alteration in visceral sensation locally at the site of presumed symptom origin in the gastrointestinal tract has been proposed as an important etiopathological mechanism in the so-called functional bowel disorders. Patients presenting with one functional gastrointestinal syndrome, however, frequently have additional symptoms referable to other parts of the gut, suggesting that enhanced visceral nociception may be a panintestinal phenomenon. We measured the sensory thresholds for initial perception (IP), desire to defecate (DD), and urgency (U) in response to rectal balloon distension, and the thresholds for initial perception and for discomfort in response to esophageal balloon distension in 12 patients with irritable bowel syndrome (IBS) and 10 patients with functional dyspepsia (FD), in comparison with healthy controls. As expected, IBS patients exhibited lower rectal sensory thresholds than controls ($P < 0.0001$), but in addition had significantly lower sensory thresholds for both perception and discomfort evoked by balloon distension of the esophagus (mean ± SEM: 8.8 ± 1.3 ml vs 12.1 ± 1.5 ml ($P < 0.05$) and 12.2 ± 1.4 ml vs 16.4 ± 1.4 ml ($P < 0.02$) respectively. Patients with FD showed similarily enhanced esophageal sensitivity, with thresholds for perception and discomfort of 8.1 ± 0.9 ml ($P < 0.02$), and 10.1 ± 1.0 ml ($P < 0.001$), respectively, but were also found to have sensory thresholds for rectal distension similar to those observed in the IBS group, significantly lower than in controls: IP 45.0 ± 17.6 vs 59.3 ± 1.5 ml ($P < 0.001$), DD 98.0 ± 17.9 vs 298.7 ± 9.0 ml ($P < 0.0001$), U 177.2 ± 25.4 vs 415.1 ± 12.6 ml ($P < 0.0001$). Somatic nerve sensory thresholds showed no significant differences between the patient and control groups. Our findings indicate that alterations in visceral sensitivity in functional gastrointestinal disease affect sites in the gut other than the putative organ of symptom origin, supporting the concept of generally enhanced visceral awareness in patients with functional bowel disorders.

KEY WORDS: visceral sensation; sensory thresholds; irritable bowel syndrome; functional dyspepsia.

Despite the high prevalence of so-called functional gastrointestinal disease (1, 2) and its extensive investigation, the underlying alterations of function remain for from clear. In relation to two of the most frequently encountered disorders, irritable bowel syndrome (IBS) and functional dyspepsia (FD), much interest has centered on the importance of motility abnormalities that can be demonstrated in the lower and upper gastrointestinal tract, respectively (3–6). Patients presenting with one functional gastrointestinal syndrome, however, frequently have symptoms referable to other parts of the gut (7, 8) or to other systems [eg, the urinary tract (9)], suggesting that a more generalized pathophysiological disturbance may

Manuscript received September 24, 1994; revised manuscript received February 23, 1995; accepted April 21, 1995.

From the Department of Medicine, Royal Infirmary, Edinburgh, Scotland.

Address for reprint requests: Dr. K.C. Trimble, Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, Scotland.

be present. In addition to the colon, alterations in the motor function of the esophagus (10), and the small intestine (11) have been demonstrated in patients with IBS. Similarly, motility abnormalities in patients with FD are not exclusive to the stomach (12). Changes in gut motility, however, have proved disappointingly nonspecific in providing an insight into the origin of symptoms in patients with functional gastrointestinal disease (13, 14), and in recent years the attention of many has shifted to the afferent limb of the enteric nervous system.

Evidence that functional gastrointestinal disorders are characterized by abnormal perception of normal events is now considerable. A lowered threshold for the perception of rectosigmoid distension in patients with IBS has been clearly documented (15, 16), and others have found that IBS patients more readily perceive the occurrence of physiological motor activity within the gut (17). Altered visceral sensation at the site of presumed symptom origin in the gut has also been implicated in the stomach in FD (18, 19), and in the esophagus in the case of both noncardiac chest pain (20, 21) and the irritable esophagus (22, 23). We hypothesized that these abnormalties of visceral nociception might not be site-specific, but rather reflect a generalized disorder of visceral sensory function in this group of disorders. We chose to explore this hypothesis in patients with IBS and FD by measuring sensory thresholds for balloon distension of the proximal and distal gastrointestinal tract in both groups and comparing these with healthy controls.

MATERIALS AND METHODS

Twelve patients with IBS (nine females, age range 19–53 years) and 10 patients with FD (seven females, age range 23–57 years) were recruited from outpatients. The clinical history taken from all patients included enquiry about both upper and lower gastrointestinal symptoms. All IBS patients met the Rome criteria (24) for the diagnosis of IBS and, where appropriate, had had investigation to exclude organic disease. FD was defined on the basis of the recommendations of an international working party (25) and was diagnosed only after a negative upper gastrointestinal endoscopy and ultrasound examination. Patients having reflux-like dyspepsia required the further investigation of ambulatory esophageal pH-monitoring to be normal before FD was diagnosed. All patients discontinued any medications for IBS or dyspeptic symptoms for at least two days prior to study; patients taking psychotropic drugs were excluded. Control data for esophageal and somatic sensory thresholds were obtained from 15 healthy volunteers (five females, age range 24–54 years), and for rectal sensory thresholds from 32 healthy volunteers (24 females, age range 24–81 years). All control subjects were recruited unpaid from hospital staff and their relatives and had no history of gastrointestinal disease. Although there were significantly more males in the esophageal control group, we found no correlation of any sensory threshold measured in the study with either gender or age.

Rectal sensitivity to balloon distension was assessed [after the method of Varma and Smith (26)] using a highly compliant latex balloon 8 cm in length and of unrestricted diameter fashioned from a condom bound to nondistensible polyvinylchloride tubing. The balloon was introduced into the empty rectum and inflated progressively via a pump with water at 37°C at a rate of 2 ml/sec. Subjects were instructed beforehand to report the first perception of rectal filling, the sensation of a desire to defecate, and the sensation of rectal urgency at the maximum tolerated volume; the balloon volume at these three thresholds was recorded. The balloon was then deflated by reversal of flow direction in the pump. Reproducibility for this technique has been established (26).

Esophageal sensory thresholds for balloon distension were measured using a perfused multilumen manometry catheter (Arndorfer ESM3) adapted so that a latex balloon 3 cm in length was positioned around the third of five recording ports, as previously described (27). Balloon length did not alter during inflation, and there were no significant differences in *in vivo* balloon compliance measured between the three subject groups. Although *in vivo* assessment of possible effects of esophageal resistance deforming the balloon was not made, a previous study has found little deforming of similar balloons inflated in the esophagus (20). The physical characteristics of the balloon assembly were tested at intervals during the studies and found not to alter with time and repeated use. The balloon catheter, connected to a low-compliance constant water perfusion pump was passed transnasally into the esophagus. The position of the lower esophageal sphincter (LES) in each subject was determined by a station pull-through technique and in each case the center of the balloon was positioned 10 cm proximal to the LES and the catheter fixed in position by taping to the nasal bridge. A routine static esophageal manometric study was first performed using a standard technique (28). For the studies of esophageal sensory thresholds, subjects were positioned in such a way as to ensure they were unaware of the occurrence or timing of balloon inflation. Rapid inflations (within 2 sec) of the balloon with air were carried out by hand from a syringe in sequential 1-ml increments for 10 sec at intervals of approximately 20 sec; the balloon was fully deflated between inflations. The interval between balloon inflations was varied from time to time to avoid anticipatory effect. Subjects were asked to report the initial perception of any sensation in the chest, abdomen, or back and to indicate the occurrence of discomfort, but were given no other instructions or prompting during the study. Studies were terminated at the reporting of discomfort by the subject. Reproducibility of balloon distension with respect to sensory threshold reporting was assessed in a sample of patients ($N = 8$) and normal controls ($N = 7$) by repeating the studies 5 min later and was found to have a mean variability of 7.9% (±2.0%) for both initial perception and discomfort thresholds, according to reproducibility data for this technique reported by ourselves and others (20, 27, 29).

In order to assess if any differences in sensory thresholds observed in the gut were specific to visceral sensory function or a reflection of a generally heightened sensitivity to noxious stimuli and to attempt to control for differences in perception that might occur as a result of possible greater anxiety in the patient groups, we also measured sensory thresholds for initial perception and discomfort evoked by a somatic stimulus. An electrocutaneous stimulus from a constant current generator (Mystro MS25, Medelec Ltd., Surrey, England) was applied to the index finger of the nondominant hand at 1 pulse/sec (100 μsec) in increments from 0 to 100 mA. Subjects were asked to report perception of and the occurrence of discomfort evoked by the stimulus. Variability within subjects for this technique was again found to be <10% for both thresholds.

All three provocative studies were performed on fasting patients on the same day, and in the order esophageal, somatic, and rectal. Results are expressed as mean and standard error of the mean, and the statistical significance of differences between study and control subjects assessed using the Mann-Whitney U statistic. Ethical approval for the study was obtained from the institution's ethics committee.

RESULTS

Three of 12 patients presenting with symptoms of IBS also admitted to symptoms referable to the upper gastrointestinal tract on direct questioning. One complained of current upper abdominal bloating, one of a past history of epigastric discomfort, and one of occasional nausea. Four of 10 patients presenting with dyspepsia had symptoms referable to the colon; two had occasional urgency of defecation, one had abdominal discomfort relieved by defecation, and one reported the passage of mucus. None of these patients, however, fulfilled the Rome criteria for the diagnosis of IBS. No patient exhibited any abnormality of esophageal motility as assessed by the static manometric study.

Figures 1–3 show the data for initial perception (IP), desire to defecate (DD), and urgency (U), respectively, in response to rectal balloon distension in healthy controls (N = 32) and in patients with IBS (N = 12) and FD (N = 10). All three rectal sensory thresholds were significantly lower in IBS patients than in controls (mean ± SEM); IP 50.8 ± 19.1 vs 59.3 ± 1.5 ml, DD 95.0 ± 20.5 vs 298.0 ± 9.1 ml, and U 176.2 ± 25.8 vs 415.0 ± 12.6 ml ($P < 0.0001$ for all). Patients with FD had sensory thresholds in the rectum very similar to those of IBS patients, again significantly lower than those of controls; IP 45.0 ± 17.6 vs 59.3 ± 1.5 ml ($P < 0.001$), DD 98.0 ± 17.9 vs 298.7 ± 9.0 ($P < 0.0001$), U 177.2 ± 25.4 vs 415.1 ± 12.6 ml ($P < 0.0001$). Statistical analyses include outliers.

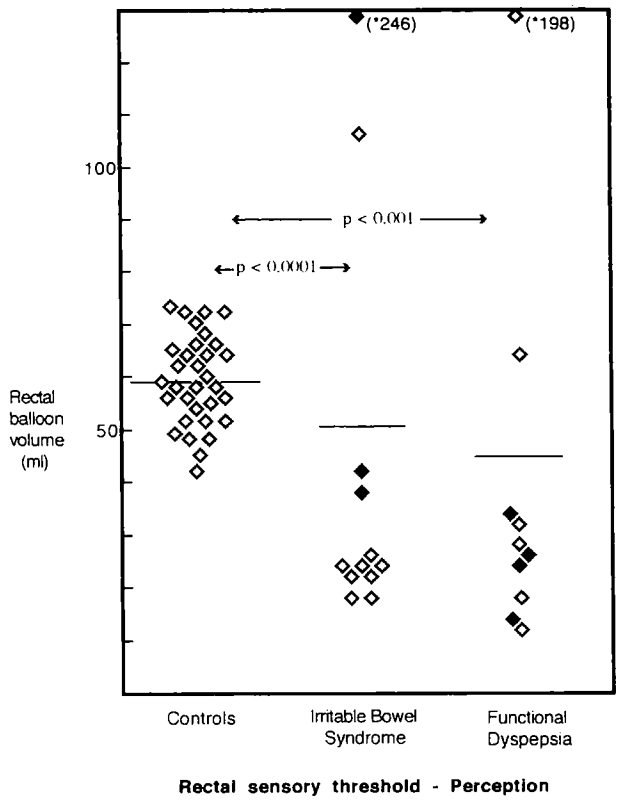

Fig 1. Individual subject data (with means) of sensory thresholds for the perception of rectal filling in response to balloon distension in healthy controls and in patients with IBS and FD. Closed diamonds denote IBS patients with additional upper gastrointestinal symptoms and FD patients with additional lower gastrointestinal symptoms. (note difference in scale in Figures 2 and 3).

The sensory thresholds for perception and discomfort by esophageal balloon distension in controls (N = 15), IBS patients, and FD patients are shown in Figures 4 and 5. Patients with FD have lower sensory thresholds in the esophagus than healthy controls. Mean and SEM values for perception and discomfort are 8.1 ± 0.9 vs 12.1 ± 1.5 ($P < 0.02$), and 10.1 ± 1.0 vs 16.4 ± 1.4 ($P < 0.001$), respectively. IBS patients show similarily enhanced esophageal sensitivity with thresholds of 8.8 ± 1.3 for perception and 12.2 ± 1.4 for discomfort ($P < 0.05$ and $P < 0.02$, respectively, compared to controls). Within the IBS patient group, the individual values for esophageal and rectal discomfort (DD) thresholds were correlated (r = 0.6, $P < 0.05$), those patients having the lowest thresholds for rectal sensitivity also tended to have the lowest for the esophagus.

Although numbers are small, no clear pattern emerges from the data on patients with one functional syndrome who have symptoms overlapping into another. IBS patients with additional upper gastroin-

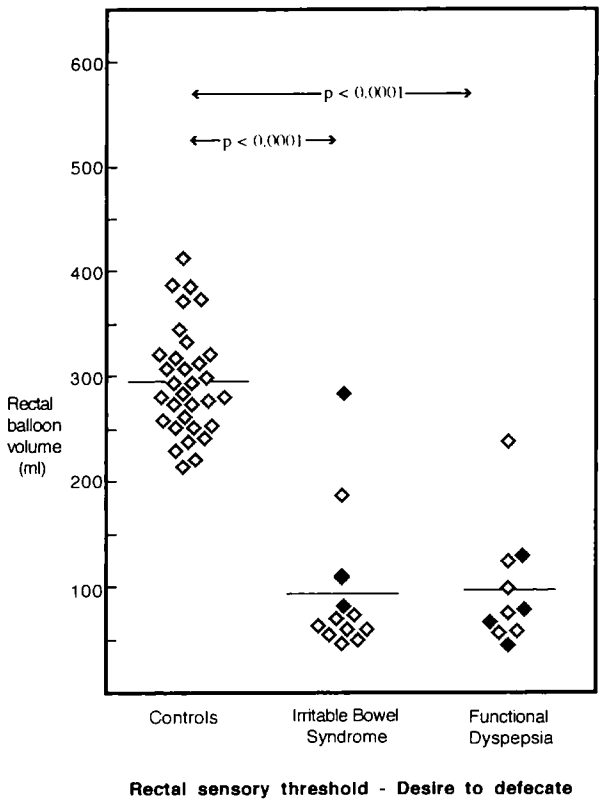

Fig 2. Individual subject data (with means) of sensory thresholds for the sensation of a desire to defecate in response to rectal balloon distension in healthy controls and in patients with IBS and FD. Closed diamonds denote IBS patients with additional upper gastrointestinal symptoms and FD patients with additional lower gastrointestinal symptoms.

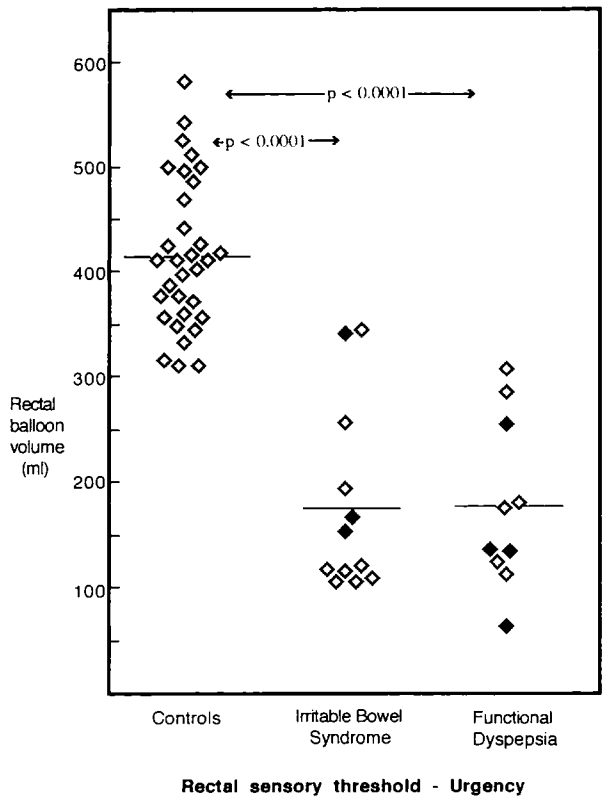

Fig 3. Individual subject data (with means) of sensory thresholds for urgency at the maximum tolerated volume in response to rectal balloon distension in healthy controls and in patients with IBS and FD. Closed diamonds denote IBS patients with additional upper gastrointestinal symptoms and FD patients with additional lower gastrointestinal symptoms.

testinal symptoms do not tend to have the lowest esophageal sensory thresholds of this group, and the rectal sensory thresholds for FD patients with symptoms referable to the colon are similar to those with upper gastrointestinal symptoms only. Separate analysis of the data from only those patients with pure IBS or FD symptoms again demonstrated significant differences from controls for all the visceral sensory thresholds measured.

In contrast to the data on visceral sensory thresholds, the results for perception and discomfort evoked by electrocutaneous stimulation (Figure 6), show that somatic sensory thresholds in patients with functional gastrointestinal disorders and healthy controls (N = 15) are similar. Interestingly, mean thresholds for perception and discomfort are slightly higher in FD patients than in controls; 21.1 ± 3.4 vs 15.9 ± 1.5, and 54.4 ± 7.3 vs 44.7 ± 4.3, but these differences did not achieve statistical significance (P = 0.07 and P = 0.13, respectively).

DISCUSSION

The results of our study clearly demonstrate that patients with IBS and FD have lowered thresholds for the perception of visceral stimuli that are not confined to the region of the gastrointestinal tract from which their presenting symptoms are presumed to emanate. The finding of enhanced sensitivity to luminal distension of a distant site within the gut in patients with IBS accords with the findings of another recent study (30) in which esophageal sensory thresholds were measured. These authors found that, as with studies of noncardiac chest pain (20), lowered sensory thresholds in the esophagus were independent of any motor disorder or alteration in motility consequent on balloon inflation, suggesting the presence of altered mechanisms of pain perception in the esophagus. The present study extends these findings in IBS patients demonstrated to have enhanced rectal sensitivity and also suggests coherence in the degree of perceptual awareness within different parts of the

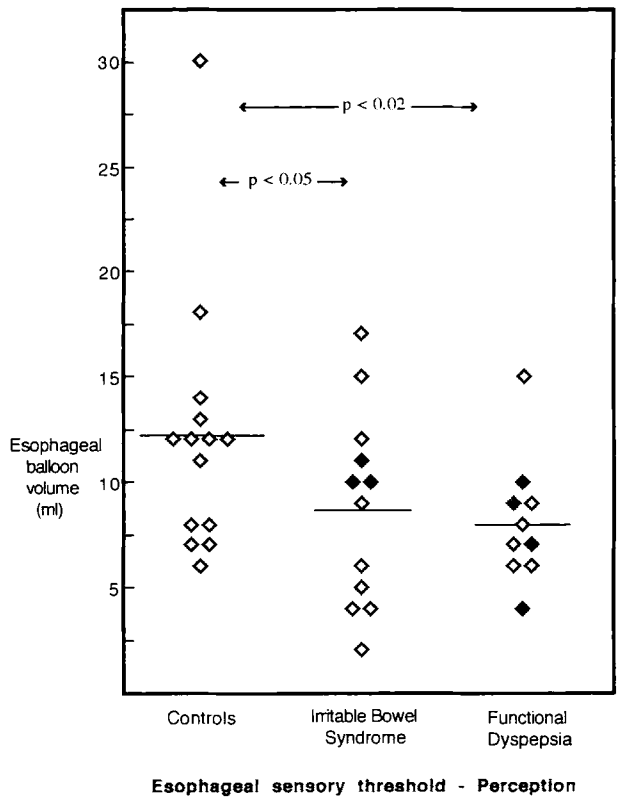

Fig 4. Individual subject data (with means) of sensory thresholds for perception of esophageal balloon distension in healthy controls and in patients with IBS and FD. Closed diamonds denote IBS patients with additional upper gastrointestinal symptoms and FD patients with additional lower gastrointestinal symptoms.

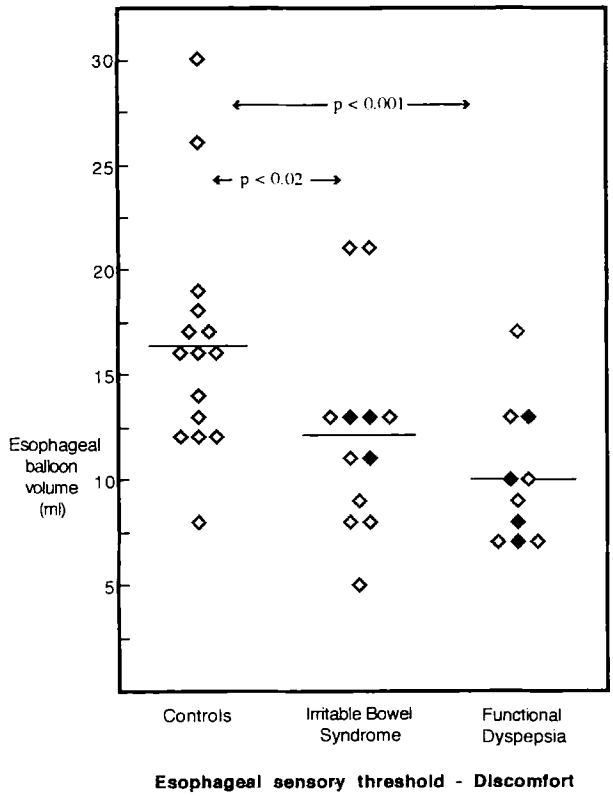

Fig 5. Individual subject data (with means) of sensory thresholds for discomfort evoked by esophageal distension in healthy controls and in patients with IBS and FD. Closed diamonds denote IBS patients with additional upper gastrointestinal symptoms and FD patients with additional lower gastrointestinal symptoms.

gastrointestinal tract in a given individual—compelling evidence for an "irritable gut" in IBS. In addition, however, our study also demonstrates a similar lack of site specificity to alterations of visceral sensory function in patients with functional dyspepsia. Patients with FD have been previously shown by two groups to have lowered thresholds for the perception of gastric distension (18, 19), and enhanced perception of small intestinal distension in FD has also been reported (31), although a recent study of duodenal sensation does not concur (32). Our results provide further evidence for a panintestinal abnormality of sensory function in FD, with sensory thresholds in both the esophagus and rectum very similar to those we have recorded for patients with IBS.

The finding of enhanced intestinal perception at distant sites in patients presenting with both upper and lower functional gastrointestinal symptoms might not be a surprising one. The necessarily symptom-based classification of functional gastrointestinal disorders (33) clearly means that case definition in patients with overlapping symptoms may be imprecise. The prevalence of additional gastrointestinal symp-

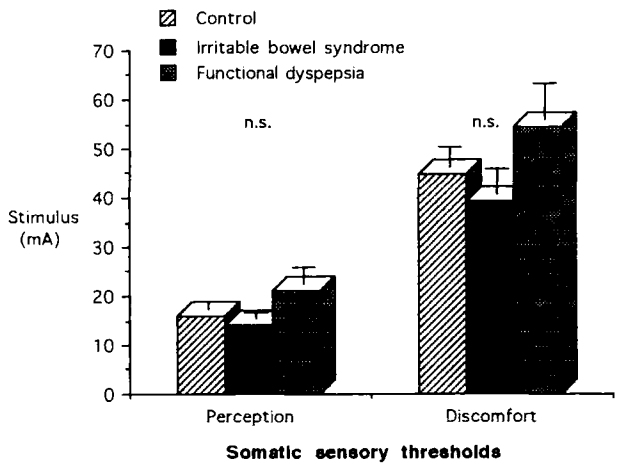

Fig 6. Histogram showing mean (and SEM) somatosensory thresholds for perception and discomfort in response to electrocutaneous stimulation in healthy controls and patients with IBS and FD.

toms in our patients accords with that reported elsewhere (34, 35). Despite this, the majority of the patients we studied had no symptoms referable to sites in the gastrointestinal tract other than those of their presenting syndrome, but nevertheless exhibited enhanced visceral sensation at both ends of the gut. Unlike Costantini et al (30), who reported that among the IBS patients they studied, those with esophageal symptoms tended to have the lowest esophageal sensory thresholds, we found no such trend in our patients with either IBS or FD.

A nonspecific effect of a generally low pain threshold in patients with functional gastrointestinal disease is unlikely to explain the differences in sensory thresholds evoked by distension of the gut observed in our patients. No significant differences were found between either IBS or FD patients and healthy controls with respect to the thresholds for reporting perception or discomfort from the application of electrical stimuli to somatic afferents. This dissociation of visceral from somatic sensitivity both in patients with IBS and FD accords with similar findings of others with respect to IBS, where no difference in tolerance for ice-water hand immersion between IBS patients and healthy controls was observed (15) or where IBS patients demonstrated higher pain thresholds than controls in response to electrocutaneous stimulation (36). In the context of this latter study by Cook et al (36), our finding of a trend toward higher somatic sensory thresholds in patients with FD, although not statistically significant, is intriguing.

The mechanism for enhanced perception of visceral stimuli in functional gastrointestinal disorders remains unclear. Accumulated evidence (15, 20, 37) suggests that the phenomenon is not simply secondary to perception of motor events evoked at the site of the stimulus or to peripheral modulation of afferent input by local changes in muscle tone or compliance. It has been proposed (37) that central modulating influences from the CNS may effect alterations in the function of visceral afferents, resulting in their upregulation. Alterations in the central processing of signals are also likely to be involved (38). Our findings indicate that whatever the mechanism of their occurrence, changes in visceral sensory function are not confined to discrete regions within the gut, even in patients with apparently site-specific symptoms.

In conclusion we have found that patients with IBS and FD exhibit enhanced awareness of provocative intestinal stimuli and lower thresholds for evoked visceral discomfort that are not confined to the region of the gut from which their symptoms are considered to derive. These abnormalities are specific to visceral sensory pathways. Just as alterations in motor function throughout the gastrointestinal tract have been previously recognized in functional bowel disease, so our findings support the concept of a panintestinal disturbance in the physiology of visceral perception in these disorders.

REFERENCES

1. Talley NJ, Zinsmeister AR, van Dyke C, Melton LJ: Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 101:927–932, 1991
2. Thompson WG: Non-ulcer dyspepsia. Can Med Assoc J 130:565–569, 1984
3. Latimer P, Sarna S, Campbell D, Latimer M, Waterfall W, Daniel EE: Colonic motor and myoelectrical activity: A comparative study of normal subjects, psychoneurotic patients and patients with the irritable bowel syndrome. Gastroenterology 80:893–901, 1981
4. Trotman IF, Misiewicz JJ: Sigmoid motility in diverticular disease and the irritable bowel syndrome. Gut 29:218–222, 1988
5. Malagelada JR, Stanghellini V: Manometric evaluation of functional upper gut symptoms. Gastroenterology 88:1223–1231, 1985
6. Waldron B, Cullen PT, Kumar R, Smith D, Jankowski J, Hopwood D, Sutton D, Kennedy N, Campbell FC: Evidence for hypomotility in non-ulcer dyspepsia: A prospective multifactorial study. Gut 32:246–251, 1991
7. Talley NJ, Piper DW: The association between non-ulcer dyspepsia and other gastrointestinal disorders. Scand J Gastroenterol 20:898–900, 1985
8. Thompson WG, Heaton KW: Functional bowel disorders in apparently healthy people. Gastroenterology 79:283–288, 1980
9. Whorwell PJ, Lupton PW, Erduran D, Wilson K: Bladder smooth muscle dysfunction in patients with irritable bowel syndrome. Gut 27:1014–1017, 1986
10. Whorwell PJ, Clouter C, Smith CL: Oesophageal motility in the irritable bowel syndrome. Br Med J 282:1101–1102, 1981
11. Kellow JE, Phillips SF, Miller LJ, Zinsmeister AR: Dysmotility of the small intestine in irritable bowel syndrome. Gut 29:1236–1243, 1988
12. Bassoti G, Pelli MA, Morelli A: Duodenojejunal motor activity in patients with chronic dyspeptic symptoms. J Clin Gastroenterol 12:17–21, 1990
13. McKee DP, Quigley EMM: Intestinal motility in irritable bowel syndrome: is IBS a motility disorder? Dig Dis Sci 38:1761–1772, 1993
14. Mearin F, Malagelada JR: Upper gut motility and perception in functional dyspepsia. Eur J Gastroenterol Hepatol 4:615–621, 1992
15. Whitehead WE, Holtcotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, Shabsin HS, Schuster MM: Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 98:1187–1192, 1990
16. Ritchie J: Pain from distention of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 14:125–132, 1973
17. Kellow JE, Eckersley GM, Jones MP: Enhanced perception of

physiological intestinal motility in the irritable bowel syndrome. Gastroenterology 101:1621–1627, 1991
18. Mearin F, Cucala M, Azpiroz F, Malagelada J-R: The origin of symptoms on the brain-gut axis in functional dyspepsia. Gastroenterology 101:999–1006, 1991
19. Bradette M, Pare P, Douville P, Morin A: Visceral perception in health and functional dyspepsia. Dig Dis Sci 36:52–58, 1991
20. Richter JE, Barish CF, Castell DO: Abnormal sensory perception in patients with esophageal chest pain. Gastroenterology 91:845–852, 1986
21. Cannon RO, Benjamin SB: Chest pain as a consequence of abnormal visceral nociception. Dig Dis Sci 38:193–196, 1993
22. Vantrappen G, Janssens J, Ghillebert G: The irritable oesophagus—a frequent cause of angina-like pain. Lancet 1:1232–1234, 1987
23. Trimble KC, Pryde A, Heading RC: Altered oesophageal sensory thresholds in patients with symptomatic but not excess gastresophageal reflux—a demonstration of the "irritable oesophagus." Gut 34(4):S18, 1993, (abstract)
24. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G: Functional bowel disease and functional abdominal pain. Gastroenterol Int 5:75–91, 1992
25. Heading RC: Definitions of dyspepsia. Scand J Gastroenterol 26(suppl. 182):1–6, 1991
26. Varma JS, Smith AN: Reproducibility of the proctometrogram. Gut 27:288–292, 1986
27. De Caestecker JS, Pryde A, Heading RC: Site and mechanism of pain perception with oesophageal balloon distention and intravenous edrophonium in patients with esophageal chest pain. Gut 33:580–586, 1992
28. Benjamin SR, Richter JE, Cordova CM, Knuff TE, Castell DO: Prospective manometric evaluation with pharmacologic provocation of patients with suspected esophageal motility dysfunction. Gastroenterology 84:893–901, 1983
29. Barlow JD, Thompson DG: Reproducibility of perception to oesophageal distention. Gut 35(suppl 2):S8, 1994
30. Costantini M, Sturniolo GC, Zaninotto G, D'Inca R, Polo R, Naccarato R, Ancona E: Altered esophageal pain threshold in irritable bowel syndrome. Dig Dis Sci 38:206–212, 1993
31. Greydanus MP, Vassallo M, Camillieri M, Nelson DK, Hanson RB, Thomforde GM: Neurohormonal factors in functional dyspepsia: Insights on pathophysiological mechanisms. Gastroenterology 100:1311–1318, 1991
32. Coffin B, Azpiroz F, Guarner F, Malagelada JR: Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. Gastroenterology 107:1345–1351, 1994
33. Drossman DA, Thompson WG, Talley NJ, Funch-Jensen P, Janssens J, Whitehead WE: Identification of sub-groups of functional gastrointestinal disorders. Gastroenterol Int 3:159–172, 1990
34. Talley NJ: Symptom patterns in functional dyspepsia. Eur J Gastroenterol Hepatol 4:597–601, 1992
35. Watson WC, Sullivan SN, Corke M, Rush D: Incidence of oesophageal symptoms in patients with irritable bowel syndromes. Gut 17:827, 1976
36. Cook IJ, Van Eeden A, Collins SM: Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. Gastroenterology 93:727–733, 1987
37. Mayer EA, Raybould HE: Role of visceral afferent mechanisms in functional bowel disorders. Gastroenterology 99:1688–1704, 1990
38. Smout AJPM, De Vore MS, Castell DO: Abnormalities of cerebral potentials evoked by esophageal distention in patients with non-cardiac chest pain. Gastroenterology 98:A393, 1990