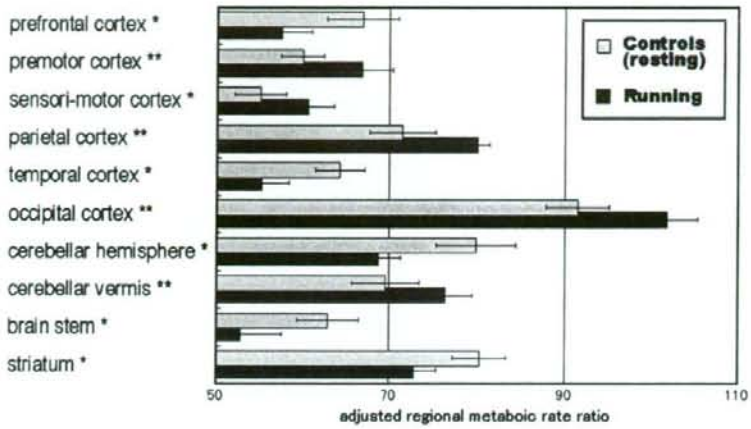

Fig. 6. Relative glucose metabolic differences between Controls (resting) and Running subjects demonstrated in terms of adjusted regional glucose metabolic rate ratios. Brain regions of statistically significant difference are shown in this figure. In all areas, $p < 0.001$, compared Controls (resting) and Running subjects. Symbols: "Z score >4.0, 'Z > 3.0. Modified from Ref. [1] by courtesy of Minerva Medica.

8. Regions of interest (ROIs) analysis

Activation in specific brain regions is associated with a certain task. For exercise, these are the motor cortex, premotor cortex, striatum, cerebellum, and a host of sensory and automatic systems. Investigators might have even specific *a priori* hypotheses regarding a specific neural network. In such cases, it is possible to examine the regional brain activity directly. The most exact and reliable way to do this analysis is to first coregister as a reference the PET image to the MRI T1 image of the same subject. Then, the investigators can directly analyze the glucose consumption of specific brain regions.

An automated ROI analysis is also available. This enables the reliable quantitative estimation of rGMR values when SPM only gives the significance of the difference in rGMR values [42]. In this method, standardized ROIs are defined on a mean MRI template image representing the brain anatomy in accordance with the Montreal Neurological Institute (MNI) space. As this method is based on a common stereotactic space (i.e., spatially normalized parametric images), operator-induced errors in defining ROIs individually for each subject can be avoided. The ROIs can be defined on the mean MRI template, there, as in the study by Kemppainen et al. [2].

9. What the study results mean

Using [^{18}F]FDG-PET technique, Tashiro and coworkers have demonstrated the relative increase in glucose uptake in the temporo-parietal association cortex, occipital cortex, premotor cortex, primary sensorimotor cortex and the cerebellar vermis [1]. Relative reduction of glucose uptake was detected in the prefrontal cortex, temporal cortex, cerebellar hemisphere, brain stem and striatum. Mean values of global brain glucose uptake was relatively lower in runners than in resting controls [1]. Kemppainen and coworkers also demonstrated significant reduction of regional glucose metabolic rate in all cortical regions in correlation to exercise intensity, especially in the dorsal part of the anterior cingulate cortex [2]. Interestingly, they also pointed out that exercise training could be related to adaptive metabolic changes in the frontal cortex [2]. Thus, global and regional brain metabolic decline was observed using [^{18}F]FDG-PET especially in the limbic and frontal regions [1,2]. It is easy to explain the metabolic increase in the regions directly associated with execution of exercise task, while it is not so easy to explain the mechanism of relative decrease in the regions not involved in exercise. The relatively low glucose uptake detected in the cerebellar hemisphere in the study by Tashiro and coworkers was brought about by the adaptation due to the repetition of the same motor task [9], while the cause of the reduced metabolism in the prefrontal cortex and limbic regions was not known at that moment. Previous imaging studies in anxiety disorders demonstrated increased glucose metabolism in these regions [43,44]. We speculated that the frontal and limbic hypometabolism was associated with emotional changes in runners, including the phenomenon called "runner's high", a sensation of well-being and reduced anxiety during running [45].

Dietrich and Sparling reported that endurance exercise tended to impair prefrontal-dependent cognitive ability in healthy young male volunteers [46]. Based on this finding and others, Dietrich has proposed a new theory to explain the hypometabolism especially in the prefrontal region [47]. According to Dietrich's transient hypofrontality theory (THT), the prefrontal activity is suppressed indirectly due to the limitation in energy supply to the brain through blood in the situation where enormous amount of energy is needed for execution of endurance exercise [47]. Interestingly, this theory also explains a neural mechanism regarding the mental health benefits of exercise [46,47]. Here, it is of interest to also point out that Kemppainen and coworkers have suggested that substrates other than glucose, most likely lactate, are used by the brain as energy source in order to compensate the increased energy demand to maintain neuronal activity during high intensity exercise, since lactate availability during exercise tended to correlate negatively with the brain glucose uptake measured with [^{18}F]FDG-PET in their study [2].

10. Conclusion

PET neuroimaging in the field of sports science is a relatively new research field. An advantage of [^{18}F]FDG-PET method is that subjects do not have to be scanned at the same time than during the exercise. We showed the feasibility of using FDG-PET in monitoring relative changes in the activity of different brain regions induced by running. This technique supplies further evidence to support the positive aspects of exercise in the fields of sports

physiology and psychology. We anticipate that this technique would become a useful tool in sports medicine in the investigation of human physiological and psychological response to exercise.

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Contributions of Pain Sensitivity and Colonic Motility to IBS Symptom Severity and Predominant Bowel Habits

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OBJECTIVES: **Irritable bowel syndrome (IBS) patients show pain hypersensitivity and hypercontractility in response to colonic or rectal distention. Aims were to determine whether predominant bowel habits and IBS symptom severity are related to pain sensitivity, colon motility, or smooth muscle tone.**

METHODS: **One hundred twenty-nine patients classified as IBS with diarrhea (IBS-D, N = 44), IBS with constipation (IBS-C, N = 29), mixed IBS (IBS-M, N = 45), and unspecified IBS (IBS-U, N = 11) based on stool consistency, and 30 healthy controls (HC) were studied. A manometric catheter containing a 600-mL capacity plastic bag was positioned in the descending colon. Pain threshold was assessed using a barostat. Motility was assessed for 10 min with the bag minimally inflated (individual operating pressure [IOP]), 10 min at 20 mmHg above the IOP, and for 15-min recovery following bag inflation. Motility was also recorded for 30 min following an 810-kcal meal.**

RESULTS: **Compared with HC, IBS patients had lower pain thresholds (medians 30 *vs* 40 mmHg, $P < 0.01$), but IBS subtypes were not different. IBS symptom severity was correlated with pain thresholds (rho = −0.36, $P < 0.001$). During distention, the motility index (MI) was significantly higher in IBS compared with HC (909 ± 73 *vs* 563 ± 78, $P < 0.01$). Average barostat bag volume at baseline was higher (muscle tone lower) in HC compared with IBS-D and IBS-M but not compared with IBS-C. The baseline MI and bag volume differed between IBS-D and IBS-C and correlated with symptoms of abdominal distention and dissatisfaction with bowel movements. Pain thresholds and MI during distention were uncorrelated.**

CONCLUSIONS: **Pain sensitivity and colon motility are independent factors contributing to IBS symptoms. Treatment may need to address both, and to be specific to predominant bowel habit.**

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INTRODUCTION

There is no consensus on the pathophysiology of irritable bowel syndrome (IBS). In several studies, IBS patients had lower perception thresholds and increased sensations of discomfort to intraluminal distention in the sigmoid colon (1–3) and the rectum (4–6) (visceral hypersensitivity), or more exaggerated GI motility responses to experimental stress (7, 8), phasic intraluminal distention (9, 10), or eating (11, 12) (hyperreactive motility) compared with healthy controls (HC). However, there are only limited data on the extent to which visceral hypersensitivity and hyperreactive motility correlate with each other and influence clinical symptoms of abdominal pain and altered bowel habits (13).

Some reports suggest that patients with diarrhea-dominant IBS (IBS-D) have increased visceral sensitivity compared with those with constipation-dominant IBS (IBS-C) (14, 15), but others failed to find differences between subtypes (16, 17). Previous reports may be inconsistent because of a small number of subjects or other methodological differences. The guidelines for subclassifying IBS into IBS-C and IBS-D were recently revised (18). The former Rome II criteria (19) used multiple signs and symptoms to make this subclassification, which were complex and possibly unreliable, but the Rome III criteria simplified this classification by using only stool consistency (18). Most patients with IBS have a stool frequency within the normal range regardless of bowel pattern (20), but stool consistency (from watery to hard) reflects intestinal transit time (21). In this study, we used the Rome III criteria to identify subtypes of IBS.

Aims of this study were to: (a) compare IBS patients to HC with respect to pain sensitivity and tonic and

phasic colon motility, (b) determine whether IBS subtypes defined by usual stool consistency differ on these variables, (c) determine whether pain sensitivity is related to (*i.e.*, correlated with) phasic and tonic motility, and (d) determine whether IBS symptom severity is related to pain sensitivity, or tonic or phasic colon motility.

METHODS

Subjects

This was a prospective study. Subjects were recruited by advertisements or physician referrals and screened by telephone. The study population consisted of 136 patients who fulfilled Rome II criteria for IBS, received a physician diagnosis of IBS, and had current symptoms (abdominal pain or discomfort at least one-fourth of the time in the last 3 months). These subjects had no history of gastrointestinal surgery (other than appendectomy or cholecystectomy), inflammatory bowel disease, celiac disease, lactose malabsorption, heart disease, or diabetes mellitus, and they were not pregnant at the time of study.

Patients with IBS were classified by usual stool consistency into subtypes according to Rome III guidelines (18): IBS-D was defined as loose (mushy) or watery stool $\geq$25% and hard or lumpy stool <25% of bowel movements, and IBS-C was defined as hard or lumpy stool $\geq$25% and loose or watery stool <25% of bowel movements. IBS with mixed bowel habits (IBS-M) was defined as loose or watery stools $\geq$25% of the time plus hard or lumpy stools $\geq$25% of the time, and IBS with normal bowel habits (IBS-U, for unclassifiable) was defined by neither loose/watery nor hard/lumpy stools 25% or more of the time. The Rome III descriptions of stool consistencies were adapted from the Bristol Stool Scale, but the pictures of different stool forms were not provided to subjects.

The control population was recruited by advertisement and consisted of 33 subjects without any significant or recurring gastrointestinal symptoms. Exclusion criteria were average stool frequency of less than 3 per week or more than 3 per day, abdominal pain, or use of a laxative or antidiarrheal agent on more than two occasions over the prior year, history of alcohol or substance abuse, a psychiatric diagnosis, or any of the medical conditions listed above for the IBS patients. The study was approved by the Institutional Review Board of the University of North Carolina (UNC), and all subjects provided written informed consent.

Study Design

Subjects were admitted to the General Clinical Research Center at the University of North Carolina for a 24- to 30-h period. They were asked to fast for at least 4 h prior to reporting for admission. On the day of admission, a medical history, physical examination, and breath test for lactose intolerance and small intestinal bacterial overgrowth were completed. The Irritable Bowel Syndrome Severity Scale (22) (IBS-SS), the Brief Symptom Inventory-18 (23) (BSI-18), and other questionnaires were completed on a computer terminal during the breath test. A low-fiber meal was consumed at approximately 5:00 p.m. Day 1 ended with a bowel cleanout consisting of 1.5 oz of Fleet's phosphosoda consumed at 6:00 p.m. and repeated at 9:00 p.m.

QUESTIONNAIRES. The IBS-SS (22) is a validated scale for measuring the overall severity of IBS symptoms. It consists of five equally weighted questions. Subjects are asked to indicate for the past 10 days the average intensity of abdominal pain, the number of days with any abdominal pain, the average severity of abdominal distention, dissatisfaction with bowel habits, and the degree to which bowel symptoms interfered with their usual activities. Response to all except the pain frequency question are on a 1–100 numeric scale ("none" to "worst ever"), and the number of days of pain in the past 10 days is multiplied by 10 to arrive at a 0–100 score for this item. The five questions are added to arrive at a total score of 0–500.

The BSI-18 (23) is a validated questionnaire for measuring the degree of psychological distress over the past week. Subjects are asked how much they were bothered by each of 18 symptoms, and they respond on a 5-point ordinal scale from "not at all bothered" to "extremely." There are three subscales—anxiety, depression, and somatization—as well as a global severity index (GSI). Sum scores for each subscale and the GSI are converted to standardized scores where the mean for the healthy population is a score of 50 and each standard deviation from the mean is equal to 10 scale points; thus, a score of 60 is one standard deviation above the mean. These standardized scores adjust for sex differences in the reporting of psychological symptoms, so BSI-18 scores for men and women can be pooled together.

EQUIPMENT. The *barostat* is a computer-controlled pump (Distender II model, G&J Electronics, Willowdale, Ontario, Canada) used for testing sensory thresholds and smooth muscle tone in the lumen of the bowel. It inflates a plastic bag to a predefined pressure and holds this pressure constant for a fixed period of time by adding or subtracting air. Volumes and pressures are recorded 16 times per second and are displayed graphically in real time. The rate of inflation and deflation was 38 mL/s. Controlling the pump by means of a computer program made it possible to present complex sequences of distentions.

The *motility catheter* (Model C7-CB-0026, Mui Scientific, Mississauga, Ontario, Canada) is 5 mm in outside diameter. It consists of a bundle of smaller polyethylene tubes bonded together and includes a central lumen that accommodates a guide wire, two lumens that open inside the bag (one to inflate/deflate the bag and a second to monitor pressure inside the bag), plus four small catheters used to measure pressures 2.5 and 5 cm from the proximal and distal edges of the bag. A disposable, 10 cm long, 600 mL capacity polyethylene bag (Model CT-BP600R, Mui Scientific) was attached to the surface of the motility catheter and tied with surgical thread.

The *pneumohydraulic pump* (eight-channel hydraulic capillary infusion system, Arndorfer Inc, Greendale, WI) uses a tank of compressed air to force degassed sterile water from a reservoir through four capillary (very small diameter) catheters that are connected to four pressure transducers. These pressure transducers are also connected to the four small catheters in the motility catheter that open above and below the barostat bag. Water is perfused through the pressure transducers and the perfusion catheters at a rate of 0.37 mL/min. Because there is a continuous column of water connecting the pressure transducer to the openings on the outside of the motility catheter, pressure changes occurring at the openings are transmitted up the column of water to the pressure transducers. The outputs of these pressure transducers were continuously recorded (see below).

The *physiological recorder* used to record phasic and tonic motility changes above and below the balloon was a Synectics Polygram (Medtronic Inc., Minneapolis, MN). This instrument continuously recorded pressure changes above and below the bag and stored them in a digital file. A research nurse marked these recordings to indicate which experimental condition was in effect.

Colonic Sensory and Motility Testing

All physiological and sensory testing was performed on day 2 according to the protocol in Figure 1. On the morning of day 2 at approximately 8:00 a.m., the barostat catheter was placed in the descending colon for sensory and motility testing. First, a guide wire was inserted to the level of the splenic flexure using a flexible sigmoidoscope. The sigmoidoscope was then withdrawn and the motility catheter was guided over this wire. The guide wire was then withdrawn and barostat placement was confirmed by fluoroscopy. Following catheter placement, the subject rested for 90 min before testing began. No sedation was used during sigmoidoscopy. Subjects were not permitted to have food until the test meal (see Fig. 1).

SAMPLE DISTENTION AND DETERMINATION OF IOP. Subjects were instructed to give separate ratings of the intensity of pain and urgency to defecate experienced at the end of each distention, using a 6-point scale (0 = no sensation, 1 = weak, 2 = mild, 3 = moderate, 4 = strong, and 5 = intense). The scale was visible to subjects during the procedure. Sample distentions were then performed during which the barostat bag was inflated in a stepwise fashion by increasing bag pressure by 4 mmHg every 15 s until the subject reported moderate pain (rating of 3). The sample distentions served three purposes: (a) to insure that the barostat bag was unfolded, (b) to teach the subject how to use the rating scale to describe the intensity of colonic sensations, and (c) to decrease anticipatory anxiety. The barostat bag was then slowly inflated with 30 mL of air and the pressure was allowed to equilibrate for 3 min. The average bag pressure during the last 15 s defined the individual operating pressure (IOP) (24), which is the minimum pressure required to overcome mechanical forces and inflate the bag with 30 mL of air. All sensory and motility testing was done with the subject lying in a left-lateral position to minimize pressures because of the weight of overlying body tissues compressing the bowel.

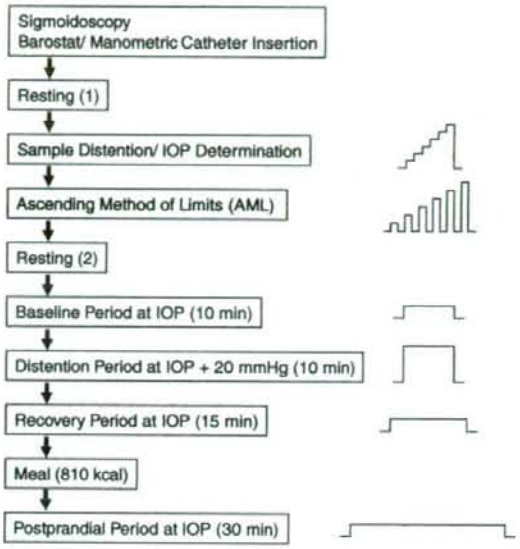

Figure 1. Study protocol. Graphs on right show sequence of pressure changes during each phase of testing. IOP (individual operating pressure) is the pressure required to overcome the weight of overlying tissue and minimally inflate the barostat bag.

ASCENDING METHOD OF LIMITS (AML). Pain thresholds in the colon were assessed using the AML (24). Phasic distentions were 30 s in duration and were separated by 30-s rest intervals. Distentions starting at the IOP and progressively increased in 2 mmHg steps until either the subject requested the research nurse to stop the protocol or 48 mmHg was reached. The pain threshold was defined as the amount of pressure above IOP at which the subject first reported moderate pain (absolute distending pressure *minus* the IOP). If the subject reached 48 mmHg without reporting moderate pain, then the pain threshold was defined as 50 mmHg *minus* the IOP. After measuring pain thresholds, there was a 15-min rest period. Individual pain thresholds are shown in Figure 2.

COLONIC PHASIC MOTILITY. Phasic contractions were measured from the perfusion ports above and below the bag under the following conditions: (a) during the fasting baseline for 10 min at the IOP, (b) during distention for 10 min at a pressure of IOP + 20 mmHg, (c) during a recovery period after intraluminal distention for 15 min at the IOP, and (d) following the meal for 30 min at the IOP. These tracings were visually screened to exclude artifact, defined as wave amplitudes less than 5 mmHg or with durations less than 6 s. The beginning

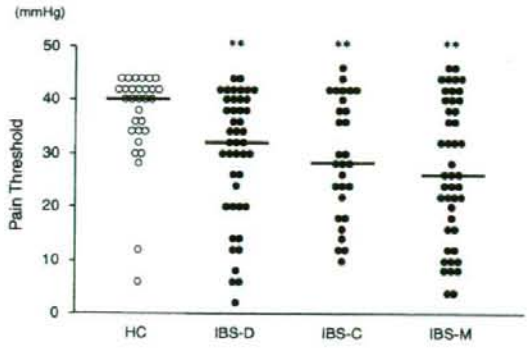

Figure 2. Pain threshold to intraluminal distention in the descending colon. Pain threshold in the descending colon was assessed using an electronic barostat by the ascending method of limit (AML). Each horizontal bar indicates the median value. The pain threshold was defined as the amount of pressure above IOP at which the subject first reported moderate pain (absolute distending pressure *minus* the IOP). If the subject reached 48 mmHg without reporting moderate pain, then the pain threshold was defined as 50 mmHg *minus* the IOP. HC = healthy controls (N = 30); IBS-D = IBS with diarrhea (N = 44); IBS-C = IBS with constipation (N = 29); IBS-M = mixed IBS (N = 45). $^{*}P < 0.05$, $^{**}P < 0.01$, *versus* controls.

and ending inflection points for each individual contraction were identified visually and the area under the curve was calculated using computer software (Polygram, Lower GI Edition, Version 5.06; Synectics Medical, now Medtronic, Inc., Minneapolis, MN). These areas were added together, then divided by recording time in seconds (excluding the time occupied by movement artifact), and multiplied by 100. The MI was the average of phasic contractions at four perfusion ports.

COLONIC TONIC MOTILITY. Average barostat bag volume in each period was recorded as a measure of smooth muscle tone (24). Muscle tone was measured during the fasting baseline, recovery period after intraluminal distention, and following the meal. The average volume required to maintain the barostat bag at a constant pressure was recorded. The average barostat bag volume in successive 5-min blocks constitutes an index of smooth muscle tone.

POSTPRANDIAL MOTILITY. The test meal was standardized and contained 810 kcals and 38 grams of fat. Subjects were asked to consume the meal within 10 min. Immediately after completing the meal, the patient returned to the prone position and bag pressure was maintained at the IOP for 30 min (the postprandial period). Phasic and tonic motility were recorded throughout this period.

Data Analysis

Phasic and tonic motility were assessed at baseline and in response to stimulation with intraluminal distention and meal ingestion. Because there were differences between groups at baseline, the response to stimulation had to be assessed after adjusting for baseline differences. To accomplish this, we expressed stimulated values as a percentage of baseline values. Absolute values are also presented in Table 2 to allow the reader to compare these two methods of data presentation. Statistical comparisons were performed on both the percent-of-baseline values and the absolute values.

Comparisons between groups were made using the Kruskal-Wallis test, followed by Mann-Whitney U-test. Correlations between variables were limited to the IBS patients, and employed the Spearman nonparametric correlation coefficient to account for nonnormal distributions of some variables. Multiple linear regression was used to determine which variables were most strongly associated with IBS symptom severity. In this analysis, dummy regression terms to code for usual stool consistency (hard or lumpy stool $\geq$25% and loose or watery stool $\geq$25%) were used (1 = yes, 0 = no). For all analyses, a P value of 0.05 without adjustment for multiple comparisons defined statistical significance.

Although this is the largest study to be reported comparing subgroups of IBS patients on physiological parameters, the subgroups were unequal in size (N = 45 for IBS-D, N = 29 for IBS-C, N = 45 for IBS-M, and N = 11 for IBS-U), and consequently the statistical power of between-group comparisons and correlations varied and could lead to spurious conclusions. Three steps were taken to avoid this: (a) no statistical comparisons were made to the IBS-U group and no correlations were reported for this subgroup because it was too small; (b) for other between-group comparisons, we identified the minimum Z-score for a Mann-Whitney U-test involving the smallest group (IBS-C) that was significant at $P < 0.05$ and interpreted other comparisons as statistically significant only if they exceeded this critical value; and (c) similarly, for Spearman nonparametric correlations, we identified the smallest correlation of a group of size N = 29 that was significant at $P < 0.05$ and interpreted other correlations as statistically significant only if they exceeded this critical value.

RESULTS

Eligible Subjects

One hundred twenty-nine IBS patients (20 men; mean age 35.8 yr) and 30 healthy control subjects (8 men; 37.2 yr) underwent both colonic sensory and motility tests. Seven additional IBS patients were enrolled but did not undergo colonic sensory and motility testing: three refused flexible sigmoidscopy, two began but could not tolerate completion of unsedated sigmoidscopy, one had an extremely elevated blood pressure, and one had colonic inflammation detected on sigmoidscopy. Three additional control subjects were similarly screened but excluded: one did not tolerate the flexible sigmoidscopy and two had exclusionary medical conditions that were detected during the study (lactose intolerance in one and prior colonic surgery in the other).

Table 1. Demographics, IBS Symptom Severity, and Psychological Distress Scales

	Controls	IBS total	IBS-D	IBS-C	IBS-M	IBS-U[¶]
Number	30	129	44	29	45	11
Women n (%)	22 (73)	109 (84)	34 (77)	26 (90)	38 (84)	11 (100)
Age (yr)	37.2 ± 2.2	35.8 ± 1.1	36.6 ± 2.0	34.9 ± 2.0	35.1 ± 1.9	38.4 ± 3.5
Race						
White	13	90	31	16	37	6
Non-white	14	36	12	12	7	5
Unknown	3	3	1	1	1	0
IBS-SS						
Overall	27.9 ± 9.8	273.2 ± 8.1[†]	255.8 ± 15.1[†]	281.1 ± 16.5[†]	282.2 ± 13.6[†]	287.9 ± 13.2
Pain severity	4.7 ± 2.4	47.0 ± 2.2[†]	43.3 ± 3.8[†]	45.5 ± 4.5[†]	48.2 ± 3.9[†]	64.4 ± 5.6
Pain frequency	4.5 ± 2.3	47.2 ± 2.1[†]	43.4 ± 3.6[†]	46.6 ± 4.5[†]	48.9 ± 3.7[†]	58.9 ± 5.1
Distention	3.3 ± 1.5	44.8 ± 2.6[†]	38.5 ± 4.7[†]	51.4 ± 5.3[†]	48.4 ± 4.1[†]	35.7 ± 8.8
Bowel dissatisfaction	18.0 ± 5.8	77.6 ± 2.2[†]	72.9 ± 4.3[†]	80.7 ± 4.0[†]	80.7 ± 3.2[†]	75.0 ± 9.1
QOL	2.7 ± 1.9	56.4 ± 2.6[†]	57.2 ± 4.6[†]	56.9 ± 5.3[†]	55.9 ± 4.1[†]	53.9 ± 11.0
BSI-18						
Global scale	42.3 ± 1.5	52.4 ± 0.8[†]	53.4 ± 1.5[†]	51.6 ± 1.6[†]	52.5 ± 1.2[†]	49.8 ± 3.6
Somatization	44.8 ± 1.2	54.1 ± 0.7[†]	55.5 ± 1.1[†]	52.8 ± 1.6[†]	53.9 ± 1.0[†]	52.9 ± 3.4
Depression	46.0 ± 1.5	51.0 ± 1.0[*]	52.6 ± 1.9[†]	52.0 ± 1.8[*]	49.4 ± 1.6	49.0 ± 5.1
Anxiety	43.3 ± 1.2	51.1 ± 0.8[†]	51.7 ± 1.4[†]	50.6 ± 1.7[†]	51.8 ± 1.4[†]	45.8 ± 2.6

[¶]No statistical comparisons were made to the IBS-U group because of a small sample size.
Data were shown as mean ± SEM.
[*]$P < 0.05$; [†]$P < 0.01$, compared with controls, Mann-Whitney U-test.
IBS-SS = IBS severity scale; BSI-18 = brief symptom index 18.

Two of 129 eligible patients did not complete the postprandial assessment because of unpleasant symptoms experienced during the test meal. One patient did not complete only the postprandial tonic motility assessment because of equipment failure. Two patients and one control subject did not report symptom severity on the IBS-SS. No serious adverse events were observed.

Table 1 shows demographic characteristics of the sample. There were no differences between HC and IBS patients in gender, age, or race/ethnicity.

IBS Symptom Severity and Psychological Distress

Scores on the IBS-SS and the BSI-18 are shown in Table 1. IBS patients scored significantly higher than HC on the IBS-SS total score and all subscales of the IBS-SS. Figure A1 in the Appendix shows IBS-SS scores for all subjects separated into groups. This figure demonstrates that the IBS-SS scores were normally distributed within the IBS subgroups and that there was no tendency for the subtypes of IBS to differ from each other. On the BSI-18, IBS patients also scored significantly higher than HC on all subscales and on the global symptom index. However, there were no significant differences among the IBS subtypes.

Pain Sensitivity

IBS patients had significantly lower thresholds for pain on the barostat test compared with HC (Table 2). Figure 2 shows the distribution of pain thresholds for each group. All IBS subtypes had significantly lower pain thresholds than HC, and for 57% of IBS patients, pain thresholds were below

Table 2. Sensory Thresholds and Colonic Motility Responses in Subtypes of IBS

	Controls (N = 30)	IBS Total (N = 129)	IBS-D (N = 44)	IBS-C (N = 29)	IBS-M (N = 45)	IBS-U[¶] (N = 11)
Pain threshold (mmHg)	40 [6–44]	30 [2–46][†]	32 [2–44][†]	28 [10–46][†]	26 [4–46][†]	36 [6–42]
Motility Index						
Baseline	280 ± 33	311 ± 19	370 ± 37	271 ± 35[§]	290 ± 32	263 ± 40
Distention	563 ± 78[‖]	909 ± 73[†,‖]	840 ± 127[*,‖]	1,001 ± 208[‖]	914 ± 99[†,‖]	927 ± 162
Recovery	302 ± 30	430 ± 31[‖]	531 ± 61[*,‖]	422 ± 65[†]	372 ± 45[†]	288 ± 40
Postmeal	429 + 49[‖]	481 + 28[‖]	542 ± 60[†]	422 ± 47[‖]	477 ± 45[§,‖]	410 ± 61
IOP (mmHg)	9.1 ± 0.6	9.3 ± 0.3	9.8 ± 0.6	9.4 ± 0.6	8.8 ± 0.5	8.4 ± 0.8
Tone (mL)						
Baseline	54.8 ± 7.9	40.1 ± 2.8[*]	32.5 ± 3.1[*]	48.7 ± 6.9[§]	38.3 ± 4.5[*]	55.3 ± 14.5
Recovery	54.2 ± 7.9	38.6 ± 2.8[*]	34.5 ± 4.0[*]	42.8 ± 5.8	36.6 ± 4.7[*]	52.2 ± 14.6
Postmeal	21.1 ± 2.5[‖]	18.8 ± 1.2[‖]	18.6 ± 1.6[‖]	20.5 ± 3.3[‖]	17.6 ± 2.0[‖]	19.6 ± 5.0

[¶]No statistical comparisons were made to the IBS-U group because of a small sample size.
Sensory thresholds are shown as medians with range and motility data are shown as means ± SEM.
[*]$P < 0.05$; [†]$P < 0.01$, compared with controls; [§]$P < 0.05$, compared with IBS-D; [‡]$P < 0.05$; [‖]$P < 0.01$, compared with each baseline, Mann-Whitney U-test.

the 95% confidence interval for controls (34 mmHg). There were no significant differences in pain thresholds between the subtypes of IBS.

Phasic Colon Motility

BASELINE. When tested under baseline conditions (fasting, no intraluminal distention), the MI (phasic contractions) was no different in the total IBS patient group *versus* HC (Table 2). However, the IBS-D group showed significantly more phasic contractions than IBS-C.

RESPONSE TO INTRALUMINAL DISTENTION. As shown in Table 2, both HC and IBS groups showed a significant increase in MI during intraluminal distention. The magnitude of this increase was greater in the IBS patients compared with HC. The magnitude of the increase in MI from baseline to distention was significantly greater in the IBS-C and IBS-M groups compared with HC ($P < 0.05$), but the subtypes of IBS did not differ from each other in magnitude of increase in phasic motility from baseline. Figure A2 in the Appendix shows responses to distention as a percentage of baseline values. Statistical analysis of these baseline-adjusted values showed the same significant comparisons as did analysis of the absolute values.

During the recovery period following intraluminal distention, the MI decreased and was not significantly different from baseline for either HC or IBS patients (all subtypes combined). When the IBS subtypes were compared with each other during recovery from distention, there were no significant differences between the subtypes.

RESPONSE TO EATING. As shown in Table 2, both HC and IBS showed significant increases in MI following the meal, but the magnitude of this increase was similar in IBS *versus* HC. There was no significant difference between IBS subtypes in the magnitude of the meal-stimulated increase in phasic contractions. Figure A2 in the Appendix shows responses to the meal as a percent of baseline values. Statistical analysis of these baseline-adjusted values also failed to show differences between HC *versus* IBS or between IBS subgroups.

Smooth Muscle Tone Measured by Barostat Bag Volume

BASELINE. When tested in the fasting state and without intraluminal distention, barostat bag volumes were smaller (*i.e.*, smooth muscle tone was greater) in IBS compared with HC (Table 2). Comparison of IBS subtypes showed that the IBS-D subgroup had significantly lower bag volumes than the IBS-C group. Because IBS-M patients, like IBS-D patients, have loose or watery stools at least 25% of the time, we performed a *post hoc* comparison of the IBS-D and IBS-M groups combined *versus* the IBS-C and IBS-U groups combined and found that this was significant; as a group, patients who reported $\geq$25% of bowel movements as loose or watery had lower barostat bag volumes (35.4 $\pm$ 2.7 mL) than IBS patients whose bowel movements were rarely loose or watery (50.5 $\pm$ 6.3 mL, $P < 0.05$).

RECOVERY PERIOD FOLLOWING DISTENTION. Muscle tone could not be measured during distention because barostat bag volumes during distention reflect compliance rather than tone. Barostat bag volumes during recovery from distention were approximately the same as during baseline and again showed lower bag volumes in the total IBS sample and in the IBS-D and IBS-M subgroups compared with the HC group (Table 2).

RESPONSE TO EATING. As shown in Table 2, both HC and IBS exhibited a statistically significant and profound decrease in bag volumes (*i.e.*, an increase in smooth muscle tone) following the meal. The magnitude of this change in bag volume was not significantly different between IBS and HC. When the IBS subtypes were compared with each other, there was no difference in muscle tone between the subtypes (Table 2). Figure A3 in the Appendix shows meal-related changes in bag volume as a percentage of baseline values. Statistical analysis of these baseline-adjusted values also failed to show differences between IBS and HC or differences between IBS subtypes.

Relationship Between Motility and Sensory Thresholds

Figure 3 shows the relationship between the MI and the threshold for pain perception. Dotted vertical and horizontal lines show where the 95% confidence interval for HC lies on each of these dimensions. The overall correlation between motility during distention and pain sensory threshold in IBS patients was rho = -0.06 ($P > 0.1$, see Fig. 3), suggesting that these are independent dimensions.

Relationship of IBS Symptom Severity to Visceral Perception, Colonic Motility, and Psychological Symptoms

When all subtypes of IBS were pooled together, the pain threshold was significantly correlated with overall symptom severity (rho = -0.36, $P < 0.001$), intensity of abdominal pain (rho = -0.34, $P < 0.001$), frequency of abdominal pain (rho = -0.32, $P < 0.001$), and severity of abdominal distention (rho = -0.31, $P < 0.001$). Neither phasic motility nor smooth muscle tone was significantly correlated with overall symptom severity or with individual symptoms on the IBS-SS. However, because there were differences in motility between IBS-D and IBS-C (as shown in Table 2), it was possible that associations between motility and clinical symptoms were obscured by pooling all IBS subtypes together. Therefore, the correlations between motility parameters and key clinical symptoms (frequency of clinical pain, intensity of abdominal distention, and dissatisfaction with bowel habits) were computed for each IBS subtype separately. These data are summarized below.

ABDOMINAL PAIN. Clinical pain frequency was significantly correlated with pain threshold in IBS-D (rho = -0.33,

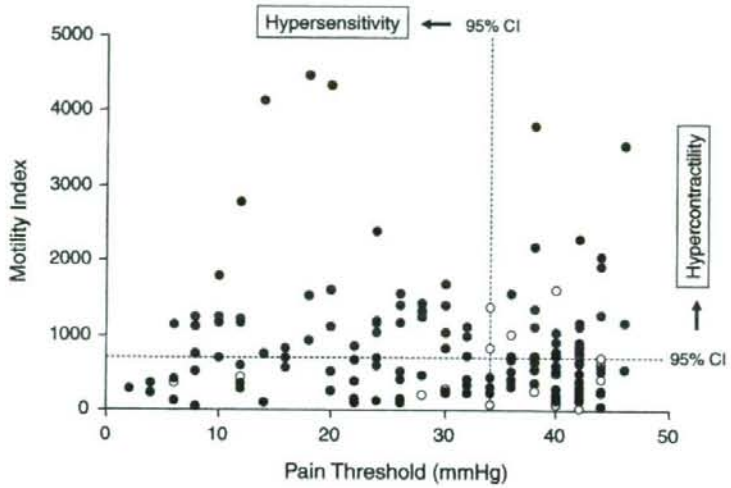

Figure 3. Relationship between colonic motility during distention period and pain threshold. No significant relationship was observed between colonic motility during distention period and visceral sensitivity in IBS patients (N = 129; closed circles) or healthy subjects (N = 30; open circles). Dashed lines show the 95% confidence intervals (CI): 49% of IBS patients showed contractile activity above the CI for controls in response to intraluminal distention, and 57% of patients had pain thresholds below the CI for controls. Of these patients, 31% showed both visceral hypercontractivity and pain hypersensitivity.

$P < 0.05$) and this correlation was even stronger in IBS-M (rho = -0.50, $P < 0.001$). However, there was no correlation between pain threshold and clinical pain frequency in IBS-C (rho = -0.13, NS).

ABDOMINAL DISTENTION. The motility index was negatively correlated with severity of abdominal distention in IBS-C (rho = -0.39, $P < 0.05$), but the motility index was unrelated to distention severity in IBS-D and IBS-M. The negative correlation indicates that as the amount of phasic contractions increased in IBS-C, the severity of distention decreased.

DISSATISFACTION WITH BOWEL HABITS. The symptom of dissatisfaction with bowel habits correlated negatively (rho = -0.40, $P < 0.01$) with postprandial smooth muscle tone in IBS-D (*i.e.*, smaller bag volumes because of greater smooth muscle tone were associated with greater dissatisfaction with bowel habits). Among IBS-M and IBS-C, there was no association with muscle tone.

PSYCHOLOGICAL SYMPTOMS. When all IBS patients were analyzed together as one group, somatization (the tendency to notice and report somatic sensations possibly indicative of disease) was significantly correlated with overall IBS symptom severity (rho = 0.30, $P < 0.01$), and with the IBS-SS subscales for pain frequency (rho = 0.23, $P < 0.05$) and abdominal distention (rho = 0.21, $P < 0.05$). Anxiety and depression were not significantly related to bowel symptoms. When the subtypes of IBS were analyzed separately, the association between somatization and bowel symptom severity was found to be significant only for the IBS-M subtype: (rho = 0.36 for pain frequency, rho = 0.30 for abdominal distention, and rho = -0.30 for dissatisfaction with bowel movements; all significant at $P < 0.05$). Depression was significantly correlated with dissatisfaction with bowel movements, but only in the IBS-C group.

Multiple linear regression (Table 3) was used to determine whether pain threshold, phasic motility, tonic motility, BSI psychological scales for somatization, depression and anxiety, and dominant stool consistency make independent contributions to IBS symptom severity after adjusting for the intercorrelations among these independent measures. Separate regression models were run for overall IBS symptom severity and the component clinical symptoms of pain intensity, pain frequency, abdominal distention severity, and dissatisfaction with bowel movements. The regression analyses showed that a significant amount of variance in IBS symptom severity was explained by these models for all dependent variables except dissatisfaction with bowel movements; the amount of variance explained (R^2) ranged from 0.22 to 0.26 for the four significant models. Pain threshold was a significant independent predictor ($P < 0.001$) in all of these models except dissatisfaction with bowel movements, and motility index during recovery was a significant predictor for pain intensity ($\beta = 0.27$, $P < 0.05$) and abdominal distention ($\beta = -0.29$, $P < 0.05$). Somatization was a significant independent predictor for overall symptom severity ($\beta = 0.23$, $P < 0.05$) and abdominal distention ($\beta = 0.24$, $P < 0.05$). For abdominal distention, having hard or lumpy stools at least 25% of the time was also a significant predictor ($\beta = 0.20$,

Table 3. Multiple Linear Regression Analyses for IBS Symptoms Severity in Patients With IBS (N = 129)

	IBS-SS Overall	Pain Intensity	Pain Frequency	Distention Severity	Bowel Dissatisfaction
R^2	0.26†	0.23†	0.22*	0.26†	0.07
Covariates (β)					
Pain threshold	−0.36‡	−0.35‡	−0.33‡	−0.35‡	0.06
Baseline MI	−0.01	−0.08	−0.12	0.18	0.08
Distention MI	0.00	0.02	0.05	−0.10	−0.03
Recovery MI	0.01	0.27*	0.15	−0.29*	0.01
Postmeal MI	−0.08	−0.18	−0.11	0.05	−0.02
Baseline tone	0.10	0.11	0.17	0.01	0.10
Recovery tone	−0.09	−0.02	−0.15	−0.12	−0.07
Postmeal tone	0.06	0.01	0.08	−0.04	−0.14
BSI somatization	0.23*	0.12	0.13	0.24*	−0.07
BSI depression	0.11	−0.04	0.03	0.03	−0.06
BSI anxiety	−0.08	−0.03	−0.06	−0.01	0.00
Hard/lumpy stools ≥25%	0.08	−0.02	0.01	0.20*	−0.13
Loose/watery stools ≥25%	−0.04	−0.07	−0.04	−0.07	−0.02

The model included the following variables: Pain threshold, phasic and tonic motility, T-scores of BSI psychological scales for somatization, depression, and anxiety, hard or lumpy stools ≥25% (yes = 1, no = 0) and loose or watery stools ≥25% (yes = 1, no = 0).
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.
IBS-SS = IBS severity scale; MI = motility index; BSI = brief symptom index.

$P < 0.05$). Smooth muscle tone was not a significant predictor in any of the models.

DISCUSSION

This large, carefully conducted study yielded three important and novel findings: First, we confirmed that visceral pain hypersensitivity is associated with (and likely contributes to) greater severity of IBS clinical symptoms, especially the frequency and the typical intensity of abdominal pain. This association was not explained by psychological influences on symptom reporting. Second, when IBS patients were divided into subtypes based on the frequency of loose or watery stools and/or the frequency of hard or lumpy stools, we found significant differences between the subtypes in both phasic and tonic motility of the descending colon (differences in phasic motility have been previously described but differences in muscle tone have not). Third, the relationship between clinical symptoms and motility differed depending on predominant bowel habits. Thus, both pain thresholds and motility have an impact on the severity of specific IBS symptoms: pain thresholds show their strongest associations with clinical pain while motility is more strongly associated with abdominal distention and dissatisfaction with bowel movements.

Hypersensitivity for Visceral Pain

Our data are consistent with a large body of research, which shows that IBS patients exhibit hypersensitivity to intraluminal distention: 57% of our IBS patients had pain thresholds that were below the normal range, that is, below the confidence interval for pain thresholds in healthy controls (Fig. 2). A strength of this study is that sensory thresholds were studied in the descending colon rather than the rectum; most previous studies of visceral perception have tested pain sensitivity in the rectum even though it is assumed that the symptoms of IBS originate predominantly from the colon or small intestine.

Pain thresholds were significantly correlated with the overall severity of IBS symptoms. Individual symptoms that correlated with pain threshold were clinical pain intensity, pain frequency, and the severity of distention. Somatization (the psychological tendency to notice and report symptoms) was also correlated with clinical pain, abdominal distention, and overall symptom severity. However, the association between pain threshold and clinical symptoms remained significant after adjusting for the correlation of clinical symptoms with somatization, anxiety, and depression (Table 3).

We observed no significant differences in pain thresholds between IBS subtypes defined by Rome III criteria. Our findings are in agreement with previous barostat studies in the *rectum* that showed no significant differences between IBS-D and IBS-C for pain thresholds (15, 25), although previous studies showed that *rectal* urge thresholds were lower in IBS-D patients compared with IBS-C patients (15, 25). Earlier studies using volume distentions, instead of pressure or tension-scaled distentions, reported lower pain thresholds in IBS-D compared with IBS-C, which is consistent with our observation that IBS-D patients have increased muscle tone compared with IBS-C (Table 2). These data extend earlier studies by showing that in the colon as well as the rectum, pressure-scaled pain thresholds are similar in IBS-D *versus* IBS-C.

Phasic Motility

Previous reports have been inconsistent as to whether IBS patients have more phasic contractions than HC under baseline conditions (*i.e.*, fasting and without stimulation by distention, stress, or exogenous hormones): there have been reports that IBS patients show more baseline motility (26, 27), less motility (28), and about the same amount (9, 10) compared

with HC. We found no difference when comparing HC to all IBS patients combined. However, the IBS-D group showed significantly more baseline contractile activity than IBS-C. We believe our results are generalizable because our study was relatively large (N = 129 IBS patients and 30 HC) and we visually identified each phasic contraction and calculated its area under the curve rather than relying on the less precise method of allowing a computer program to estimate the MI by integrating the area of all activity above an arbitrary baseline.

Sustained intraluminal distention simulates a frequently occurring physiological stimulus to the colon, namely distention of the colon by fecal material or gas. This stimulus evokes an increase in phasic motility in both HC and IBS patients, but the increase is significantly greater in IBS patients. This exaggerated response to intraluminal distention has been termed "hyperreactivity" (29), and our data suggest that it is characteristic of all IBS patients rather than being limited to one subtype. We first reported that IBS is characterized by this exaggerated response to intraluminal distention in 1980 (10) and other laboratories have replicated this observation (9). The response to distention is reversible—MI returns to baseline when the distending stimulus is removed (Table 2)—and in other studies we have shown that it is reproducible on a second occasion of testing (10). These characteristics make the response to intraluminal distention an attractive probe of motility for investigations of IBS. However, there is overlap between IBS and HC, rendering MI of limited value as a diagnostic marker for IBS.

Eating also stimulates an increase in the MI in both HC and IBS, as others have also shown (11). We did not find that the magnitude of the meal stimulation was significantly greater in IBS patients as a group compared with HC. There were no differences in postprandial stimulation of MI between IBS subgroups.

To summarize our findings with respect to phasic contractions of the colon: (a) phasic contractions increase in reaction both to intraluminal distention and eating; (b) compared with healthy controls, IBS patients show an exaggerated response to intraluminal distention but a similar response to eating; and (c) IBS-D patients have more baseline phasic motility than IBS-C, but the differences are modest and there is overlap.

Barostat Bag Volumes

Average barostat bag volumes measured at the IOP provide an indirect measure of smooth muscle tone. As previously reported (30), IBS patients have lower bag volumes than HC, indicating that IBS is associated with increased smooth muscle tone. Our data confirm this observation and extend it by showing that elevated smooth muscle tone is limited to patients with loose or watery stools at least 25% of the time. Patients with IBS-D had significantly lower bag volumes than patients with IBS-C (Table 2).

As previously reported (27, 31), barostat bag volumes decrease substantially following a meal (Table 2), indicating an increase in smooth muscle tone in the descending colon. However, the magnitude of the increase in smooth muscle tone is similar in IBS *versus* HC, and it does not distinguish patients with IBS-D from those with IBS-C. This increase in smooth muscle tone, along with the increase in phasic motility following a meal, are believed to be part of the physiological mechanism resulting in a tendency for flatus and defecation to occur shortly after a meal.

We anticipated that phasic motility and smooth muscle tone would be related to IBS symptoms, especially to dissatisfaction with bowel habits. No associations between motility and symptoms were seen when all IBS patients were considered together. However, when IBS subtypes defined by Rome III criteria were analyzed separately, we found significant but contrasting associations: (a) bowel dissatisfaction was significantly correlated with smooth muscle tone in the IBS-D group and (b) abdominal distention was negatively correlated with phasic motility in IBS-C (decreased muscle contraction associated with increased distention severity) but not IBS-D. In general, the associations between motility parameters and clinical symptoms were weaker than the associations between pain threshold and clinical symptoms, and some of these univariate associations could not be confirmed by regression analysis. Other variables such as somatization are also significant predictors of clinical symptoms in IBS.

Relationship Between Pain Sensitivity and Motility

IBS patients demonstrate both hypersensitivity and hyperreactive motility in comparison to healthy controls. These appear to be independent pathophysiological mechanisms because (a) there is no correlation between them and (b) they show different relationships to the symptoms of IBS. Pain hypersensitivity is associated with more severe clinical pain and distention but is unrelated to dissatisfaction with bowel movements, and pain thresholds do not differ between IBS-D and IBS-C. Phasic motility and smooth muscle tone, on the other hand, are greater in IBS-D than they are in IBS-C and may play a role in regulating usual or predominant bowel habits. We did not, however, find that hyperreactive motility could reliably differentiate between patients with IBS-D and those with IBS-C. The apparent independence of pain hypersensitivity and motility suggests that different etiologies—genetic, inflammatory, psychosocial, or other factors— are likely to be found for motility hyperreactivity and pain sensitivity, and different treatments or management strategies may be required.

Study Limitations

It is possible that the invasive nature of the test protocol, which required unsedated sigmoidoscopy to place the motility catheter and led subjects to anticipate pain and/or anxiety, may have biased recruitment. Consistent with this possibility, the average age of the IBS sample was 35.8 yr, which is younger than average for the IBS patients we have studied in other settings (32). Second, the prevalence of pain hypersensitivity may have been underestimated because five IBS

patients and one HC were unable or unwilling to undergo unsedated flexible sigmoidoscopy after volunteering. Both of these study limitations could have led to an underrepresentation of IBS patients with the greatest pain sensitivity, but this would not affect the conclusions that pain sensitivity and motility reactivity are independent pathophysiological mechanisms for IBS and that pain sensitivity is the more important determinant of clinical symptoms. A third limitation is that the motility parameters tested were restricted to phasic and tonic motility in the descending colon and did not include small bowel motility (33) or high-amplitude propagating contractions (34, 35). Thus, we may have overlooked motility patterns that show a stronger association with IBS symptom severity or altered bowel habits.

Significance

This study shows that both pain thresholds and motility have an impact on the severity of specific IBS symptoms: pain thresholds show their strongest associations with clinical pain while motility is more strongly associated with abdominal distention and dissatisfaction with bowel movements. Our data further suggest that pain sensitivity and motility are independent physiological mechanisms for the symptoms of IBS. The implication of these findings for clinical practice is that treatments may have to be selected based on the patient's predominant bowel habit in order to maximize clinical benefit. Furthermore, because most drugs currently approved for the treatment of IBS have a greater impact on motility than on pain, clinicians may want to supplement current drug treatments for IBS with a pain management strategy. The implication for pharmaceutical companies is that it may be advantageous to target pain sensitivity in future drug development programs.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Patients with irritable bowel syndrome (IBS) show visceral hypersensitivity or hyperreactive motility in the sigmoid colon and the rectum.

What Is New Here

- Visceral pain sensitivity in the descending colon is associated with greater severity of IBS clinical symptoms, especially abdominal pain.
- Phasic and tonic colon motility are related to predominant bowel habits and to the clinical symptoms of abdominal distention and dissatisfaction with bowel movements.
- Visceral hypersensitivity and motility are independent physiological mechanisms for the symptoms of IBS.

APPENDIX

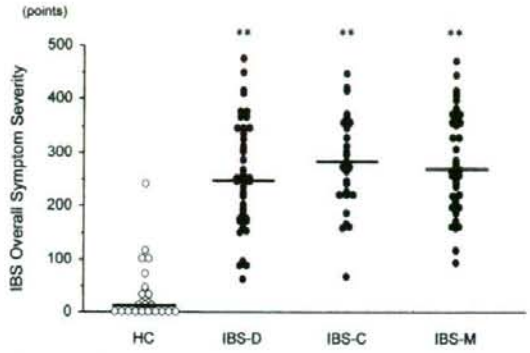

Figure A1. IBS symptom severity scale (IBS-SS) in subtypes of IBS and healthy controls. IBS-SS total score for each subject is shown. Each horizontal bar indicates the median value. HC = healthy controls (N = 30); IBS-D = IBS with diarrhea (N = 44); IBS-C = IBS with constipation (N = 29); IBS-M = mixed IBS (N = 45). $^{**}P < 0.01$, *versus* controls.

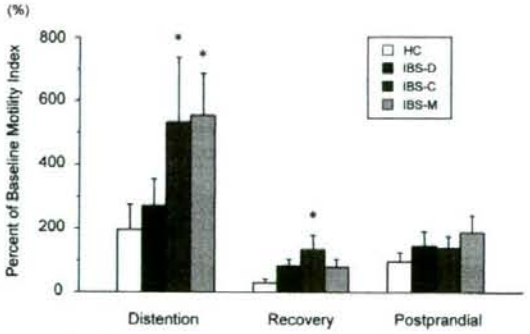

Figure A2. Changes in motility index during each stimulus period in subtypes of IBS and healthy controls. Distention, the MI during recovery and postprandial periods, is expressed as a percentage of the baseline MI for the subgroup to adjust for any baseline differences. HC = healthy controls (N = 30); IBS-D = IBS with diarrhea (N = 44); IBS-C = IBS with constipation (N = 29); IBS-M = mixed IBS (N = 45). Data were expressed as mean + SEM. $^{*}P < 0.05$ *versus* controls in same phase of testing. During distention and postprandial periods, all groups are significantly ($P < 0.05$) greater than baseline.

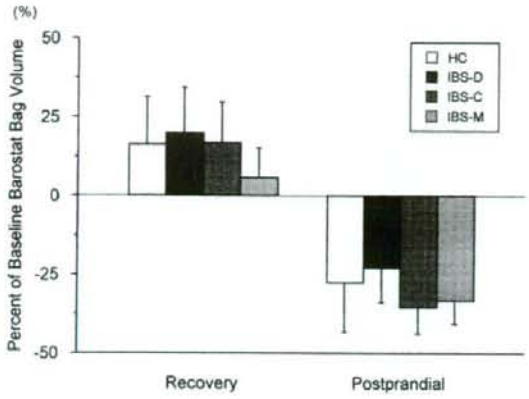

Figure A3. Changes in colonic muscle tone during each stimulus period in subtypes of IBS and healthy controls. The colonic muscle tone was measured as mean bag volume. For the recovery and postprandial periods, each bar shows percentage of baseline value for the subgroup. HC = healthy controls; IBS-D = IBS with diarrhea; IBS-C = IBS with constipation; IBS-M = mixed IBS. Data were expressed as mean ± SEM. Groups are not significantly different from each other within conditions, but postprandial values are significantly ($P < 0.05$) lower than baseline for all groups.

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CONFLICT OF INTEREST

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脳腸相関による消化管機能制御

Regulation of Gastrointestinal Function by Brain-Gut Interactions

福土 審
Shin Fukudo

生物心理社会モデルによる心身医学的なアプローチがその威力を発揮する代表的な疾患群として機能性消化管障害(functional gastrointestinal disorders)が挙げられる．過敏性腸症候群(irritable bowel syndrome；IBS)はその概念形成の源流となった疾患である．機能性消化管障害，特にIBSの研究と臨床は，既知の生物学的診断マーカーが未発見である疾患の国際的診断基準作成，脳-末梢臓器相関の概念化，脳機能画像の導入，ストレス病態からの関連物質の絞り込み，炎症と感作の関連，遺伝子と環境の関連，性差医学，薬物療法と心理療法の組み合わせなどの多くの点で他疾患に応用できる先進性を含んでいる．

key words　IBS，脳腸相関，消化管運動，内臓(消化管)知覚，PET，粘膜炎症

はじめに

現代は多くの疾患の心理面が重視される社会情勢にある．George Engelの生物心理社会モデル(biopsychosocial model)は，疾病の理解に生物学的要因だけでなく，心理社会的要因の関与も分析し，総合的に疾病を把握する試みである[1]．機能性消化管障害(functional gastrointestinal disorders)は，生物心理社会モデルがその威力を発揮する代表的な疾患群である[2]．その概念形成の源流となったのが過敏性腸症候群(irritable bowel syndrome；IBS)である[2]．機能性消化管障害，特にIBSの研究と臨床は，多くの点で先進性を含んでおり，その進歩に我が国の科学も貢献している．

後述するように，IBSは内臓機能と脳機能が関連する脳腸相関の病態を持つ．文部科学省科学技術政策研究所から，基礎研究を中心とする科学の動向(2001～2006年)を俯瞰的に示す「サイエンスマップ2006」が公表されている[3]．科学全体の中でも，"内臓感覚と情動・共感の神経機構"の研究が，最近急速に出現してきたテーマであり，勃興しつつある注目研究領域の1つであることがわかる(図1)．

I　機能性消化管障害のRome III診断基準

機能性消化管障害とは，消化器症状が慢性・再発性に持続する一方で，その症状が通常の臨床検査で検出される器質的疾患によるものではない障害である[4]．その代表的な障害がIBSである．IBSの中核の症状は腹痛とそれに関連

■図1　科学研究の動向に占める"内臓感覚と情動・共感の神経機構"の研究の位置

■表1 機能性消化管障害[2]

(A)機能性食道障害
- A1:機能性胸焼
- A2:機能性食道性胸痛
- A3:機能性嚥下困難
- A4:食道球

(B)機能性胃十二指腸障害
- B1:機能性ディスペプシア
  - B1a:食後不快症候群(PDS)
  - B1b:上腹部痛症候群(EPS)
- B2:嘔気障害
  - B2a:空気嚥下症
  - B2b:非特異過剰嘔気障害
- B3:悪心嘔吐障害
  - B3a:慢性特発性悪心
  - B3b:機能性嘔吐
  - B3c:周期性嘔吐症候群
- B4:成人反芻症候群

(C)機能性腸障害
- C1:過敏性腸症候群(IBS)
- C2:機能性膨満
- C3:機能性便秘
- C4:機能性下痢
- C5:非特異機能性腸障害

(D)機能性腹痛症候群(FAPS)

(E)機能性胆嚢・Oddi括約筋障害
- E1:機能性胆嚢障害
- E2:機能性胆道Oddi括約筋障害
- E2:機能性膵臓Oddi括約筋障害

(F)機能性直腸肛門障害
- F1:機能性便失禁
- F2:機能性直腸肛門痛
  - F2a:慢性直腸肛門痛
    - F2a1:肛門挙筋症候群
    - F2a1:非特異機能性直腸肛門痛
  - F2b:消散性直腸肛門痛
- F3:機能性排便障害
  - F3a:失調性排便
  - F3b:不適切排便推進症

(G)新生児・幼児機能性消化管障害
- G1:乳児逆流症
- G2:乳児反芻症候群
- G3:周期性嘔吐症候群
- G4:乳児腹痛
- G5:機能性下痢
- G6:乳児排便困難
- G7:機能性便秘

(H)小児・思春期消化管機能障害
- H1:嘔吐・空気嚥下症
  - H1a:思春期反芻症候群
  - H1b:周期性嘔吐症候群
  - H1c:空気嚥下症
- H2:腹痛関連機能性消化管障害
  - H2a:機能性ディスペプシア
  - H2b:過敏性腸症候群
  - H2c:腹部片頭痛
  - H2d:機能性腹痛
    - H2d1:小児機能性腹痛症候群
- H3:便秘・便失禁
  - H3a:機能性便秘
  - H3b:非貯留性便失禁

■表2 IBSのRome Ⅲ診断基準[7]

■腹痛あるいは腹部不快感が
■最近3カ月の中の1カ月につき少なくとも3日以上を占め
■下記の2項目以上の特徴を示す
- ①排便によって改善する
- ②排便頻度の変化で始まる
- ③便形状(外観)の変化で始まる

* 少なくとも診断の6カ月以上前に症状が出現し，最近3カ月間は基準を満たす必要がある．

** 腹部不快感とは，腹痛とは言えない不愉快な感覚を指す．病態生理研究や臨床研究では，腹痛あるいは腹部不快感が1週間につき少なくとも2日以上を占める者が対象として望ましい．

した便通異常であるが，大腸内視鏡検査では異常は見られない．これらの疾患群は特定の検査値によって診断できるものではないために，国，また立場や見解の相違によって診断が異なるという事態を生み，それがまた，特異的な病態生理の同定を阻むという事態を招いていた．

この事態が動いたのが1988年のRomeにおける国際消化器病学会である[2]．このときに，IBSの国際的な診断ガイドラインが提唱され，翌年に公表された．IBSが明確に定義されると，IBSに類似しているがIBSとは言えない多くの障害を同時に定義する必要が生じる．腹痛・腹部不快感のない下痢は，IBSではなく機能性下痢と定義する．また，腹痛・腹部不快感のない便秘もIBSではなく機能性便秘である．これらの疾患群が機能性腸障害であり，機能性腸障害がこのように明確に同定されると，機能性腸障害に類似しているが，症状を作り出す消化管の部位が異なる他の障害も同時に定義しなくてはならない．便通異常のない腹痛は機能性腸障害ではなく，このような患者は機能性腹痛症候群と診断すべきである．以上のような議論が様々な国の医師で構成されるワーキングチームで交わされ，最初の国際的な診断基準であるRome基準が1990年に発表され，成書として1994年に公刊された[4]．これを契機として，機能性消化管障害の診断基準統一の気運が高まり，改訂版であるRome Ⅱ基準が1999年に公表された．Rome Ⅱ基準は国際的に普及し，機能性消化管障害の診断，治療，研究，創薬などあらゆる面を活性化した[2]．

その改訂版が2006年に公刊された．これがRome Ⅲ基準である[2),4)]．その過程には日本人研究者も貢献している[5),6)]．機能性消化管障害は成人の食道，胃・十二指腸，小腸・大腸，胆道・膵管，直腸・肛門のそれぞれの部位の障害と機能性腹痛症候群の6障害(A～F)，ならびに新生児・幼児と小児・思春期の2障害(G，H)の合計8障害からなる(表1)[2),4)]．そのすべての障害の診断基準が国際的に統一されている．以上から，国，また立場や見解の相違によって診断が異なるという事態はすでに過去のものとなったと言えよう．

Ⅱ IBSのRome Ⅲ診断基準

Rome Ⅲ基準においては，IBSは表2のように定義されている[7]．また，IBSはBristol便形状尺度(表3)の頻度に基づいて4型に分類されている(表4)[2),7)]．その根拠は，排

■表3 Bristol便形状尺度[7]

型	説明
1	分離した硬い木の実のような便(排便困難を伴う)
2	硬便が集合したソーセージ状の便
3	表面にひび割れがあるソーセージ状の便
4	平滑で柔らかいソーセージ状あるいは蛇状の便
5	柔らかく割面が鋭い小塊状の便(排便が容易)
6	ふわふわした不定形の小片便,泥状便
7	固形物を含まない水様便

■表4 IBSの分類(Rome Ⅲ)[7]

❶便秘型IBS(IBS-C)
硬便 or 兎糞状便[a]が便形状が25%以上,かつ,
軟便 or 水様便[b]が便形状の25%未満[c]
❷下痢型IBS(IBS-D)
軟便 or 水様便[b]が便形状の25%以上,かつ,
硬便 or 兎糞状便[a]が便形状の25%未満[c]
❸混合型IBS(IBS-M)
硬便 or 兎糞状便[a]が便形状の25%以上,かつ,
軟便 or 水様便[b]が便形状の25%以上[c]
❹分類不能型IBS(IBS-U)
便形状の異常が不十分であって,
IBS-C, IBS-D, IBS-Mのいずれでもない[c]

a:Bristol便形状尺度1型2型
b:Bristol便形状尺度6型7型
c:止瀉薬・下剤を用いないときの糞便で評価する

便頻度よりも便形状が下部消化管機能をより反映するためである.これらの型は相互移行の頻度が70～100%に及ぶ.IBSは機能性消化管障害の原型であり,その病態も機能性消化管障害の中で最も良く分析されている.IBSは有病率が10～20%と高頻度であり,患者のQOL(quality of life)が低く,患者個人と医療全体双方の経済に悪影響を及ぼすことから重要な疾患である[2].

Ⅲ 脳腸相関

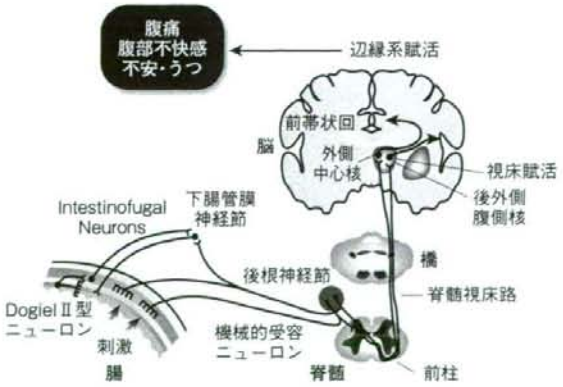
脳腸相関(brain-gut interactions)という概念[8]により,IBSの病態生理が理解されている(図2).日常臨床では"心理社会的ストレスによってIBS患者の消化器症状が発症もしくは増悪する"という現象がその典型例である[8].これは脳から腸に向かう関係である.逆に,腸から脳に向かう関係もIBSでは重要である[2].これは日常臨床では"消化管刺激に対する内臓知覚が過敏である"という現象として現れる.種々の脳機能画像により,脳腸相関が科学的かつ視覚的に分析できる.PET(positron emission tomography)あるいは機能的核磁気共鳴法(functional MRI)を用いた検討により,大腸伸展刺激時のヒト消化管知覚の脳内プロセシングと神経伝達が明らかになりつつある(図3)[9].これらの脳機能画像を用いて大腸伸展刺激時の局所脳血流量の変化を見ると,健常者で見られる前帯状回の賦活が,IBS患者ではさらに亢進しており,ときに前頭前野の賦活化が見られる[2].これらより,IBSの消化管知覚の脳内プロセシング異常が示唆される.

PETで得られたIBSの消化管知覚における脳内プロセシング異常は,大脳誘発電位によっても明らかになりつつある.大腸の拡張刺激に対する大脳誘発電位を導出すると,IBSにおいてはN_1, P_1, N_2の3相波の潜時が短く,振幅が大きく,同様の象が機能性ディスペプシア[注1]においても見られる[10].IBS患者に見られる内臓知覚過敏の重要な原因として,消化管から中枢に伝達される信号の処理過程が感作されている病理が示唆される.

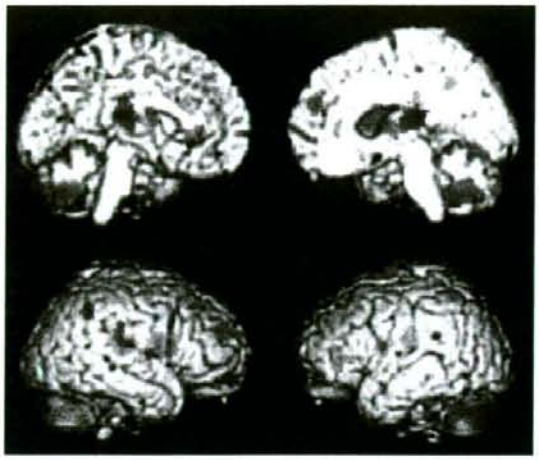
Ⅳ IBSにおけるCRHの役割

IBSの脳腸の病態生理を一元的に説明しうる有力な物質が脳と腸の双方に豊富に存在するCRH(corticotropin-releasing hormone)(図4)である[11].IBSの心理的異常としては抑うつと不安が多い[2].CRHはこれらの心理的異常と関

注1 辛いと感じる食後のもたれ感,早期飽満感,心窩部痛,心窩部灼熱感のいずれか1つ以上があり,症状の原因となる器質的疾患が上部消化管内視鏡検査を含む検査で除外されているもの.症状は6カ月以上前から生じ,最近3カ月は上記基準を満たしているもの.



■図2 脳腸相関:消化管から脳に向かう経路の模式図



■図3 内臓刺激時の脳画像（PET）
下行結腸を40mmHgで刺激したときの$H_2{}^{15}O$静注による局所脳血流．視床，島，前帯状回，前頭前野，小脳の活性化．
Hamaguchi T, et al: Neurogastroenterol Motil (2004) 16: 299-309 より転載．

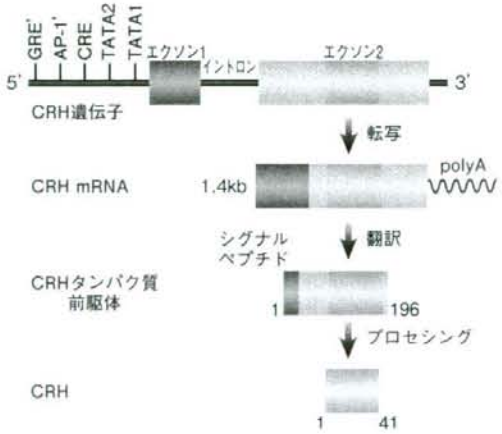
連するペプチドである．ストレスやCRH投与は消化管知覚閾値を低下させる．さらに消化管腔を刺激すると延髄の孤束核で転写因子c-fosの遺伝子発現が起こり，様々な神経伝達物質の合成酵素の脳内遺伝子発現の引き金となる．ヒトにおいて，CRH負荷により下垂体からACTH（adrenocorticotropic hormone）が放出されるのと同時に大腸運動が惹起される[11]．IBSにおいてはCRH負荷時のACTH放出と大腸運動のいずれにおいても過大な反応が生ずる[11]．これとは逆に，IBSに対するCRH拮抗薬の投与は，ストレスによる大腸運動亢進と消化器症状発現の双方を抑制する[12]．IBSでは脳波パワースペクトラ（power spectra）ならびにtopogram（二次元画像表示）においてβ-power増強，α-power減衰が見られるが[8]，CRH拮抗薬の投与はこの病態も緩和する[13]．CRHはR_1受容体を介して下部消化管運動を亢進させ，内臓知覚閾値を下げ，不安を招く[14]．R_1受容体刺激は炎症も増悪させる[15]．一方，R_2受容体の刺激は胃排出を遅延させるほか，多くの作用がR_1受容体と逆方向にある（図5）[15, 16]．

以上から，CRHはIBSの脳と消化管の双方の病態に重要な働きをしている可能性が高い．

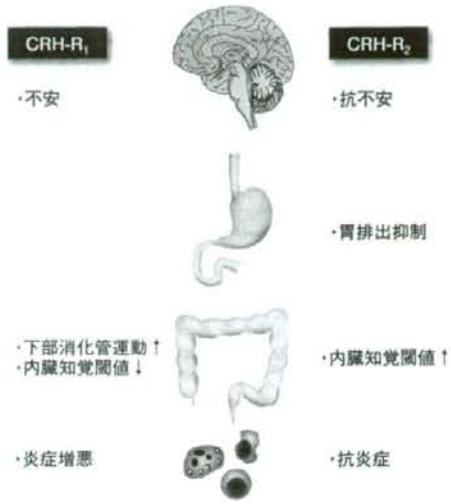
V 粘膜炎症とIBS

IBSの消化管運動・知覚異常の源流は粘膜炎症ではないかと示唆されている[16]．IBSの発症をprospectiveに検討すると，急性腸炎の患者群において，炎症がすべて消退した後にIBSが一定の割合で発症する（post-infectous IBS）[2]．IBSが発症した患者群とIBSが発症しない患者群を分ける最も大きな相違点は，急性腸炎罹患時点の心理的異常（抑うつ，不安，身体化）である．炎症性腸疾患のモデル動物でTNBS（trinitrobenzene sulfonic acid）腸炎を作り，それを回復させる．さらに，腸炎のある時期にラットにストレスを負荷した群を作る．そのうえで，筋層間神経叢の抑制性ニューロンの神経伝達物質であるノルアドレナリンの放出量を測定する．ノルアドレナリン放出量は，粘膜炎症とストレスが同時に加わったときに限って低下する．すなわち粘膜炎症があり，しかもストレスが負荷されると筋層間神経叢の機能が変化し，それが記憶される．この機序そのもの，あるいは類似の現象がIBSの根本にあるのではないかと示唆されている．

一方，どのような免疫担当細胞が筋層間神経叢の記憶の変化に関与するのかという問題がある．ヘマトキシリン-エオジン染色で正常に見えるIBS患者の大腸粘膜では上皮内リンパ球が1.8倍，$CD3^+$細胞が2倍，$CD25^+$細胞が6.5倍に増加し，免疫賦活状態にある[2]．さらに，IBS患者の終末回腸から生検したところ，健常者に比べて肥満細胞の数が増加していたという成績がある[2]．CRHやストレスは消化管運動・知覚に影響するが，それだけでなく，イオン輸送能や粘膜透過性も変化させる．これらの反応はCRH投与によって2倍以上に増加するが，CRH拮抗薬によって遮断すると，この反応も抑制される．ところがCRHを加えて肥満細胞安定化薬を投与すると，これもCRH拮抗薬と同様に反応を抑えることができる．このことから，CRHの粘膜透過



■図4 CRH遺伝子と転写翻訳プロセス



■図5 CRH-R_1, R_2の脳腸に対する作用
Fukudo S, et al: Gut (2006) 55: 146-148, Fukudo S: J Gastroenterol (2007) 42: 48-51より改変.

性亢進効果が肥満細胞を介するのではないかということ，ならびにその機構とIBSの病態の関連が注目される．

Ⅵ IBSの発症における遺伝と環境の関与

IBSは単一遺伝子の変異による疾患であるとは考えにくく，遺伝要因と環境要因を探る双生児研究がなされている[2]．双生児686組の分析では，33組（4.8%）が機能性腸障害であり，56.9%が遺伝要因，43.1%が環境要因と算定された．双生児6,060組の分析では，IBSの一致率は，二卵性で8.4%であるのに対し，一卵性では17.2%であり，遺伝性が証明された．同時に，二卵性双生児の片方がIBSである場合に他方がIBSである罹患率は6.7%であったのに対し，二卵性双生児の片方がIBSである場合に母親がIBSである罹患率は15.2%であったことから，母親の疾病行動の学習効果が示唆されている．また，IBS患者の家族歴を調査した報告では，高率に抑うつあるいは不安性障害の家族内集積があることが明らかにされている．IBSはパニック障害，性的虐待に代表される心的外傷後ストレス障害と高率に合併する[2]．IBSとストレス感受性の高さに共通する遺伝子多型・環境の両要因の検討が進行しており，セロトニントランスポーター[17]，IL-10遺伝子などが鋭意分析されている[2]．

IBSは性差医学に関しても示唆に富む疾患である[5]．妊娠可能年齢の女性IBS患者では，月経の前に消化器症状が増悪する．これは生物学的性差である．一方，心理社会的（gender）差を反映する可能性があるものに，疾患頻度がある．欧米でのIBSの女性患者対男性患者の比率は2～2.5：1で女性が高い．しかし，欧米一般人口では2：1未満となり，差が減少する．また，我が国をはじめとする東洋諸国では男女差は欧米に比較して弱い．

Ⅶ 機能性消化管障害の創薬と新たな治療法

IBSに対しては，トリメブチン，ポリカルボフィル，ロペラミド，その他の消化管に対する薬物で調整を行い，これらが奏功しないときには抗うつ薬を中心に向精神薬の使用を考慮するのが標準的な治療法である．機能性ディスペプシアに対しては，モサプリド，イトプリド，酸分泌抑制薬などを用いることが多い．機能性消化管障害に対する新たな薬物療法の開発も進んでいる[2]．CRH拮抗薬をはじめ，下痢型IBSに対する5-HT_3拮抗薬（米国アロセトロン，我が国のラモセトロン），便秘型IBSに対する5-HT_4刺激薬（米国のテガセロド），機能性便秘に対するCl^-チャネル賦活薬（米国のルビプロストン）などの創薬が活性化している．

薬物療法が奏効しない難治性のIBS患者に対しては，心理療法の有効性が科学的に立証されており，催眠療法と認知行動療法がその代表である[2]．また，我が国で開発された絶食療法はIBSの脳腸相関の再調整に有益である．

おわりに

現代は，疾患を物質レベルで追求し，科学的根拠を蓄積する医療，ならびに，患者の心理を重視し，医師-患者の関係性を重視する個体差重視の医療，これらの双方を同時に追求できるエキサイティングな時代である．患者に対する心理的な配慮は，患者に快さをもたらすから価値があるだけではなく，心身のネットワークを介した治療効果をもたらす可能性があるために価値があるのであり，IBSはそのモデル疾患であると言える．機能性消化管障害には多くの疾患があるが，解明が進んでいるのはIBSをはじめとした一部の疾患だけであり，それも不十分である．これらの疾患群全体に対する社会的認識と研究の向上が望まれる．

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