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# Dysmotility of the small intestine in irritable bowel syndrome

J E KELLOW, S F PHILLIPS, L J MILLER, AND A R ZINSMEISTER

*From the Gastroenterology Unit and Digestive Diseases Center, Mayo Clinic and Medical School, Rochester, MN, USA*

SUMMARY **Though the pathophysiology of the irritable bowel syndrome (IBS) is commonly attributed to dysfunction of the large intestine, evidence exists to incriminate the small bowel. In order to further explore the role of the small bowel in IBS several stimuli were applied, in an attempt to unmask the dysmotility of the jejunum and ileum. These included infusions of cholecystokinin-octapeptide (CCK-OP), a high fat meal, neostigmine and balloon distension of the ileum. Three groups (n=8) each of age and sex matched healthy volunteers were studied; patients with IBS complained of predominant constipation (n=8) or diarrhoea (n=8). Patients with IBS responded excessively to stimulation by CCK-OP, fatty meal, and ileal distension. In general patients with diarrhoea were more sensitive to stimuli than those with constipation. The ileum responded more to stimulation than the jejunum. As in the large bowel, stimuli appear to unmask intestinal dysmotility in patients with IBS. Motor abnormalities were often accompanied by abdominal symptoms, raising the possibility that dysfunction of the small bowel contributes to the symptoms of IBS.**

The pathophysiology of irritable bowel syndrome (IBS), although still unclear, is frequently attributed to abnormal motility of the large bowel.[1–4] Basal motor patterns in the colon may be normal, but manoeuvres which stimulate intestinal motility often unmask motor dysfunction. Stimuli implicated in this regard are gastrointestinal peptides, such as cholecystokinin;[5,6] food, especially fat;[7,8] cholinergic agonists;[9,10] and mechanical distension of the bowel.[11–13] The small intestine has also been implicated in the pathogenesis of IBS, however;[14–18] indeed, evidence exists for involvement of smooth muscle even outside the gut.[19,20]

We have reported that interdigestive cycles (MMC's) were altered in the small intestine of patients with IBS,[18] and that episodes of cramping abdominal pain often accompanied specific motor patterns in the ileocaecal region. These findings implicate dysfunction of the distal small bowel, at least in some patients with IBS. We also wondered whether provocative stimuli, if applied systematically, might disclose other disorders of motility. In the same persons[18] we defined the motor responses of the small bowel and proximal colon to CCK-OP, a high fat meal, neostigmine, and luminal distension. Each stimulus was applied to each patient; motility and symptomatic responses were compared with those of healthy subjects.[21] We reasoned that heightened sensitivity of the small bowel or proximal colon to one or more of these agents would further incriminate the midgut in the pathophysiology of IBS.

Address for correspondence: Sidney F Phillips, MD, Gastroenterology Unit, Mayo Clinic, 200 SW First Street, Rochester, MN 55905, USA.

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## Methods

### PATIENT SELECTION

Sixteen patients (10 women, mean age 34 years, range 24–49) with well established diagnoses of IBS participated. All experienced intermittent abdominal pain, an alteration of bowel habit and other features characteristic of the syndrome. Patients were matched for age (±five years) and sex, and they were categorised prospectively by the predominant alteration of bowel habit,[18] diarrhoea (n=8) or constipation (n=8). Other clinical details have been described in full previously;[18] although not

currently under active investigation or follow up, all were symptomatic. Eight healthy subjects, also age and sex matched to the patients, comprised the normal controls. All gave written informed consent to the protocol which was approved by the Mayo Clinic's Institutional Review Board and Radiation Control Committee.

### GASTROINTESTINAL MANOMETRY

Intraluminal pressures were recorded using a low compliance pneumohydraulic catheter, and two synchronised multichannel recorders (Honeywell 1600, Honeywell Test Instruments Division, Denver, CO). Pressure ports were positioned fluoroscopically, aided by the recognition of motor patterns characteristic of the different locations.[22 23] In individual subjects, two to four recording sites were positioned in the jejunum, three to six in the ileum, and one to two in the caecum and/or proximal colon. Using electronic planimetry, motility indices (MI) were calculated from each recording port. In addition to identifying the migrating motor complex (MMC), discrete clustered contractions (DCC's) in the jejunum and prolonged propagated contractions (PPC's) in the ileum, were defined as before.[22 23] Prolonged propagated contractions lasted 12–40 seconds, were of amplitude 50 to 100 mmHg and propagated rapidly, usually >60 cm/min.

### STIMULI ADMINISTERED

*CCK-OP*

CCK-OP (Kinevac, Squibb Inc, Princeton, NJ) was administered intravenously as six graded 30 minute infusions;[21] the doses spanned subphysiological to supraphysiological amounts.[21] These ranged from 2·4 (0·2) to 75·6 (3·2) pmol/kg/h (Table 1) at the point of infusion, as measured by radio-immunoassay.[24]

*Test meal*

A liquid meal (300 ml, 395 kcal, 37:49:14% fat:carbohydrate:protein) was infused over a 40 minute period through the duodenal manometry port in all IBS patients, by a peristaltic pump (Minipuls 2, Gilson, Middleton, WI). The meal was administered to four control subjects only.

*Neostigmine*

Neostigmine methylsulphate (Elkins-Sinn Inc, Cherry Hill, NJ, USA was administered as a bolus intravenous injection of one of three randomised doses: 0·25 mg, 0·5 mg, or 1·0 mg.

*Luminal distension*

The ileum was distended by a latex rubber balloon (Esco Rubber Ltd, Middlesex, England) attached circumferentially to the manometric assembly, 35 cm from the distal end. The balloon was inflated with air for one minute at one of three randomised volumes; subjects also received graded distension of the balloon. At each volume, intraballoon pressures were measured with an anaeroid pressure gauge (Tycos, Rochester, NY, USA). Placebo inflations were done in both experiments. The volume at which abdominal discomfort was first perceived was recorded.

### ADDITIONAL OBSERVATIONS

*Gall bladder contraction*

Contraction of the gall bladder (GB) was used to evaluate the responses of a recognised target organ to infusions of CCK-OP. Gall bladder volumes (GBV), in response to both CCK-OP and the test meal were monitored, using real time ultrasonography (ATL Neuro-sector, Bellevue, WA, USA) and the sum of cylinders method.[25] Details of these observations have been reported separately.[20 21]

*Symptoms*

Subjects recorded any symptoms experienced during the study in a diary and quantified the severity of abdominal pain on a visual scale (scored out of a possible grade of 10).

### EXPERIMENTAL DESIGN

Fasting motility, details of which have been reported[18] was recorded overnight, before the exogenous stimuli and the meal were administered. On the second day of study, infusions of CCK-OP were started after the passage of phase 3 of an MMC through the proximal jejunum. Motility indices were quantified during a 60 minute control period of intravenous saline and for the 180 minutes during which the sequential doses of CCK-OP were infused. Gall bladder scans were done three times in the control period and at 10 minute intervals during the infusions, simultaneous with 10 minutely assessments of motility indices.[20 21]

As CCK-OP abolished the fasting motility cycle, administration of the test meal, which followed the CCK-OP infusions, was delayed until the interdigestive motility pattern (evidenced by an MMC) had been re-established for at least 60 minutes. At this time, the GB was also shown to have refilled after CCK-OP by ultrasonography. Infusion of the meal started after passage of Phase 3 of an MMC through the proximal jejunum; motility was analysed for 60 minutes before and 180 minutes after the meal. Gall bladder scans were obtained before the meal, and postprandially at 10 minute intervals for 120 minutes, simultaneously with quantification of 10 minutely motility indices.

Neostigmine stimulation followed the meal. It was

administered immediately after a jejunal MMC, but only after the interdigestive pattern had been re-established for at least 60 minutes. Subjects were randomly assigned to one of three doses: two controls and four IBS patients received 0·25 mg; four controls and eight IBS, 0·5 mg; and two controls and four IBS, 1·0 mg. Motility was recorded for 60 minutes before and 60 minutes after the injection, and 10 minute motility indices were determined.

Luminal distension was then carried out, initially with a single volume (10 ml, two controls, four IBS; 15 ml, four controls, eight IBS; 20 ml, two controls and four IBS) and subsequently with step wise graded volumes. Inflation was for one minute at 2·5 ml increments to a maximum volume of 20 ml, at which level the balloon diameter was approximately 3·5 cm.

### DATA ANALYSIS AND STATISTICAL METHODS

In order to summarise the data within each subject and to compensate for small differences in the actual amounts of CCK-OP administered between subjects (Table 1), intestinal and GB responses to CCK-OP and to the meal were evaluated as in previous reports.[20,21] Briefly, after transformation of a 'crude' motility index to a logarithmic function (MI), a relative MI (RMI) was computed from each recording port at each (log) dose of CCK-OP, and at each 10 minute interval postprandially. Relative motility index was the log of the stimulated motility index (MI) minus the median basal (log) MI, divided by the median basal (log) MI.

Gall bladder volumes during CCK-OP and after the meal were normalised by converting to relative GBV, the actual GBV at each step divided by the median basal GBV. Doses of CCK-OP which produced 10%, 50%, and 90% reduction in GBV were estimated, designated as $D_{est}$ 10% (or 50%, or 90%, respectively) relative GBV. Those which produced a 90% reduction in GBV were associated with abdominal symptoms and were considered to be 'pharmacological'.[21] The minimum postcibal GBV, designated min pc relative GBV, was used as an index of the response of each subject's GB to the test meal.[21]

These estimated parameters and derived values were then summarised in terms of the mean (SE) values in the patient and control groups. Within group comparisons of an estimated parameter (or a derived value) against zero were based on the one-sample t-test (adjusting for multiple comparisons within sets of parameters). Between group comparisons were based on one-way analysis of variance. Relative motility indexes in response to CCK-OP were compared between groups at the $D_{est}$ 10% (50% and 90%) relative GBV; RMI's in response to the meal were compared at the min pc relative GBV.[21] The groups were compared as to the time when symptoms appeared during the infusions of CCK using a proportional hazards regression analysis.[26]

The effect of neostigmine on RMI was analysed using a two-way analysis of variance (drug dose by group). Numbers of subjects with pain in each group at each volume of balloon distension were compared using the Fisher's Exact Test (adjusted for multiple comparisons).

An alpha-level of 0·05 was considered statistically significant, while p-values between 0·05 and 0·1 were considered as of borderline statistical significance.

Table 1 *Concentrations of CCK-OP actually infused**

| *Dose level†* | *Diarrhoea‡* | *Constipation‡* | *Normal subjects* |
|---|---|---|---|
| (i), 5·0 | 2·8 (0·2) | 2·1 (0·1) | 2·2 (0·1) |
| (ii), 10·0 | 5·5 (0·3) | 4·4 (0·2) | 4·6 (0·2) |
| (iii), 20·0 | 11·1 (0·8) | 8·6 (0·4) | 9·6 (0·3) |
| (iv), 40·0 | 20·9 (1·1) | 17·4 (1·2) | 18·5 (0·9) |
| (v), 80·0 | 40·5 (1·4) | 34·8 (2·1) | 37·0 (1·0) |
| (vi), 160·0 | 85·4 (2·6) | 68·3 (4·3) | 73·2 (2·7) |

*Assayed at the point of infusion, in pmol/kg/h (mean (SE)), by radioimmunoassay for the carboxy-terminal region of gastrin-CCK peptides; †Dose of CCP-OP included in the delivery system (pmol/kg/h); ‡Patients with irritable bowel syndrome.

## Results

### BASAL MOTILITY

During fasting, all groups showed regular cycles of the MMC; however, cycle lengths were different among the two groups of IBS patients and the normal subjects.[18] Basal, fasting motility indices were not different among the groups, though certain motor patterns, were more common in IBS than in health, and these patterns were often associated with abdominal symptoms.[18]

#### *Motor responses to CCK-OP*

CCK-OP abolished MMC's in all patients; fasting patterns were replaced by apparently random pressure waves, similar to 'phase 2' or the fed state. Qualitatively the responses to CCK-OP featured increased numbers of tonic rises in base-line pressure, but usually there was little change in the numbers of phasic pressure waves (Fig. 1). In the ileum and colon, prolonged high pressure waves (PPC's) were recorded from eight IBS patients and two normal subjects (Figure 1, Table 2). These pressure waves were often accompanied by spontaneous complaints of abdominal pain; six IBS patients and one normal subject experienced symptoms concurrent with PPC's (Table 2). Figure 2

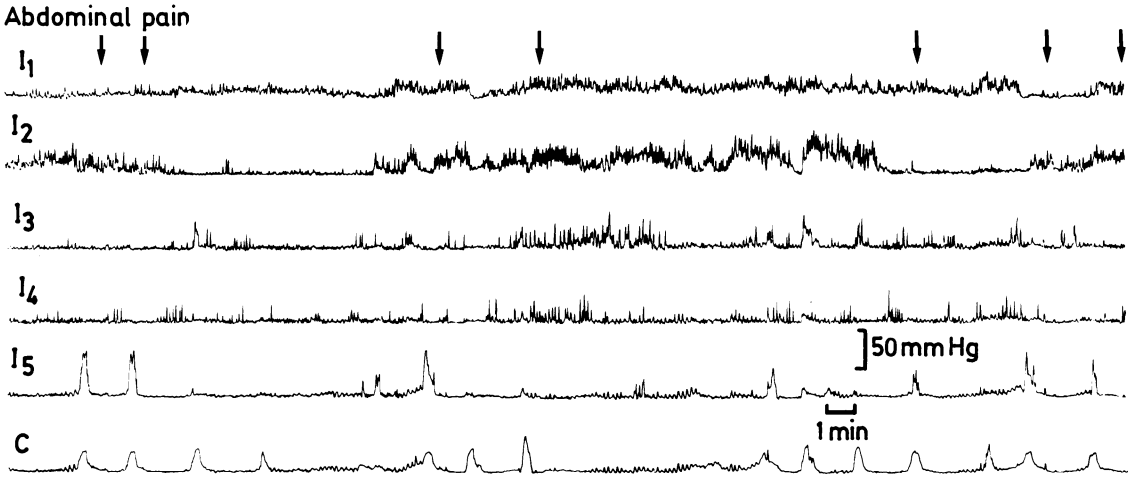


Fig. 1 *Intraluminal pressures recorded from five ileal sites ($I_1$–$I_5$) and the proximal colon during infusion of CCK-OP (at dose level 2, see Table 1) in a patient with irritable bowel syndrome. Note the tonic elevation of the baseline (two proximal channels) and spontaneous complaints of abdominal pain in association with high pressure waves (PPC's) in the distal ileum and colon.*

Table 2 *Incidence of prolonged propagated contractions (PPC's) in response to CCK-OP and neostigmine*

| | *Subjects (n)* | |
|---|---|---|
| | *With PPC's* | *With concurrent symptoms* |
| CCK-OP infusions | | |
| IBS | | |
| Diarrhoea (n=8) | 3 | 2 |
| Constipation (n=8) | 5 | 4 |
| Control (n=8) | 2 | 1 |
| Neostigmine injections | | |
| IBS | | |
| Diarrhoea (n=8) | 5 | 5 |
| Constipation (n=8) | 7 | 7 |
| Control (n=8) | 5 | 4 |

shows an ileal response to CCK-OP in which the number of phasic waves was also increased.

In the absence of high pressure waves, less well defined abdominal symptoms (distension, borborygmi, discomfort) were volunteered by all persons during infusions of the higher doses of CCK-OP. Such symptoms commenced earlier, however ($p<0{\cdot}01$) in the constipation group (84 (11) min, at dose level iii in Table 1) than in normal subjects (137 (6) min, level v) or IBS with diarrhoea (109 (14) min, level iv).

Relative motility indexes were compared for the small bowel and colon at the doses of CCK-OP equivalent to three levels of gall bladder contraction, the 10, 50, and 90% decrements of relative GBV

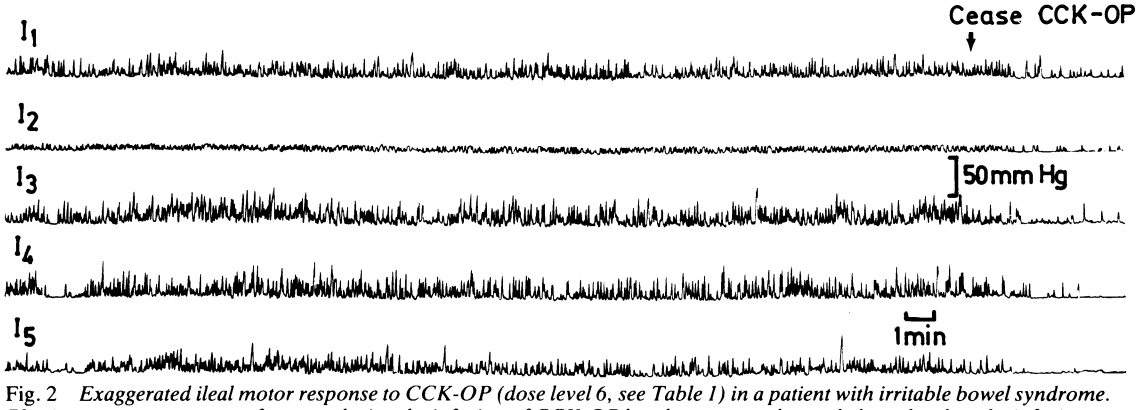


Fig. 2 *Exaggerated ileal motor response to CCK-OP (dose level 6, see Table 1) in a patient with irritable bowel syndrome. Phasic pressure waves were frequent during the infusion of CCK-OP but the patterns changed abruptly when the infusion was completed.*

Table 3 *Mean RMI at three intestinal sites in response to infusions of CCK-OP*[1]

| Site | %Reduction* in RGBV | Controls | IBS-constipated | IBS-diarrhoea |
|---|---|---|---|---|
| Jejunum† | 10 | −0·03 (0·03) | 0·03 (0·03) | 0·01 (0·02) |
| | 50 | 0·05 (0·02) | 0·03 (0·03) | 0·05 (0·03) |
| | 90 | 0·12 (0·04) | 0·07 (0·03) | 0·27 (0·06)‡ |
| Ileum | 10 | 0·01 (0·02) | −0·01 (0·03) | 0·01 (0·04) |
| | 50 | 0·05 (0·07) | −0·04 (0·04) | −0·01 (0·05) |
| | 90 | 0·17 (0·08) | −0·03 (0·03) | 0·22 (0·04)‡ |
| Colon | 10 | −0·04 (0·06) | 0·02 (0·08) | −0·01 (0·03) |
| | 50 | −0·05 (0·06) | −0·05 (0·07) | −0·01 (0·03) |
| | 90 | 0·05 (0·06) | −0·04 (0·08) | 0·16 (0·08) |

*Relative motility index, RMI, at steps in the CCK-OP dose response curve closest to the 10, 50, and 90% levels of gall bladder contraction for each individual; †Differences among subject groups by multivariate analysis at 10, 50, and 90% RGBV significant for jejunum only ($p<0·05$); ‡Different from zero ($p<0·05$, adjusted for three comparisons).

(Table 3). In the jejunum, at 90% relative GBV, RMI's were increased for all groups of subjects. In addition, there were differences among groups for all dosage levels ($p<0·05$, multivariate analysis at 10, 50, and 90% relative GBV); IBS with constipation had lesser and IBS with diarrhoea had greater RMI's than did the control group. Similar differences in RMI's were also seen in the ileum ($p=0·06$, multivariate analysis) and less so in the proximal colon ($p=0·10$). Patients with diarrhoea always displayed the greater motor responses to CCK-OP, though differences from zero were only significant with the higher doses of CCK-OP, those which produced 90% reduction in relative GBV (Table 3).

*Responses to test meal*

Migrating motor complexes were abolished in all subjects and replaced by motor activity typical of the 'fed' state. The duration of the postprandial pattern did not differ among the three groups.[18] No consistent trends in RMI's over time were detected in any group during the postprandial period; at the min pc relative GBV, RMI's were not significantly different between IBS and controls at any site. Controls showed no significant increase in RMI at any site; however, in IBS, RMI's were increased in the small bowel (Figs 3 and 4), and patients with diarrhoea showed greater responses than did those with constipation. Relative motility indexes of the proximal colon did not change postprandially in any group.

*Responses to neostigmine*

An increase in the number and amplitude of random contractions was observed in most subjects in the jejunum, ileum, and proximal colon after each dose of neostigmine; there were no differences at any level of the bowel between IBS and controls.

In the ileum, multiple PPC's started within several minutes of administration of neostigmine in 12 IBS patients and five control subjects (NS), most of which

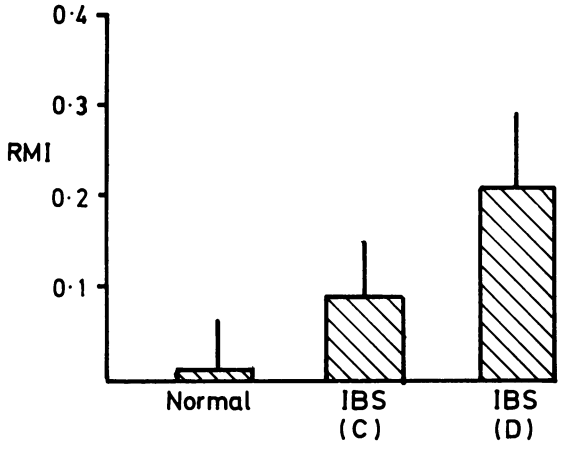


Fig. 3 *Jejunal motility response to a high fat meal in control subjects and patients with irritable bowel syndrome (IBS) with constipation (C) or diarrhoea (D); group means (SE). RMI is the relative motility index, postprandial motility minus basal motility divided by basal motility. Group differences were not significant. Normal subjects and constipated groups not different from zero; for the group with diarrhoea, p=0·05, when adjusted for three comparisons.*

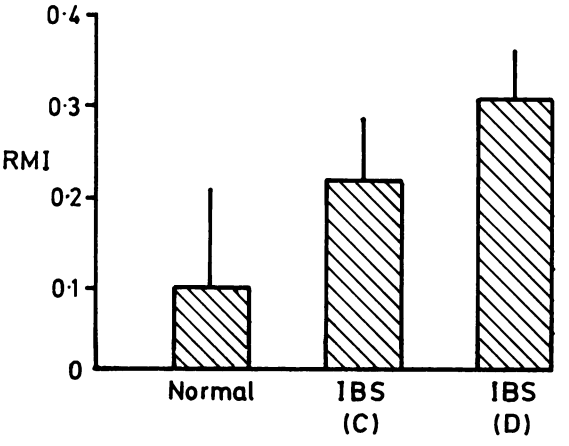


Fig. 4 *Ileal motility response to a high fat meal in control subjects and in patients with irritable bowel syndrome (IBS) with constipation (C) or diarrhoea (D). RMI (group means (SE)) is the relative motility index; postprandial motility minus basal motility divided by basal motility. Group differences were not significant; normals showed no augmentation (not different from zero, p>0·05), but both groups of IBS had augmented postprandial motility (p<0·05), adjusted for three comparisons.*

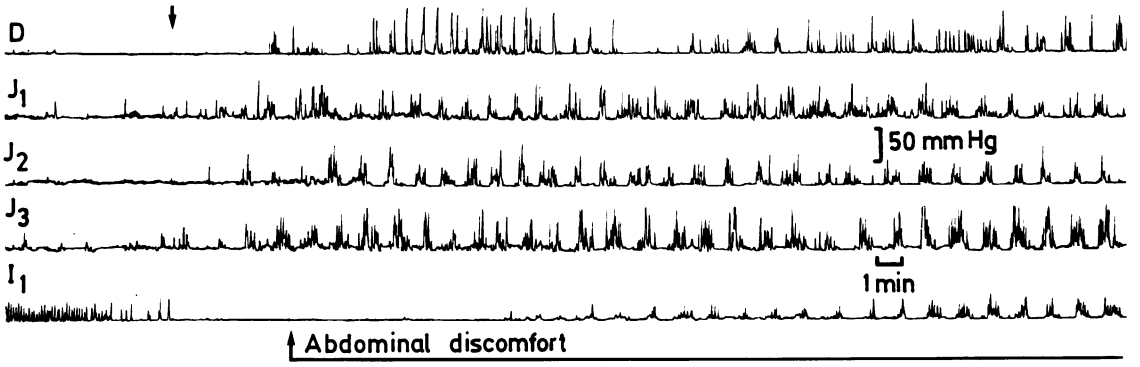


Fig. 5 *Jejunal motility recorded as intraluminal pressures from one duodenal, three jejunal and one ileal site after neostigmine (arrow). Note the presence of multiple clustered groups of phasic contractions affecting the jejunum and, to the right of the tracing, the ileum.*

were symptomatic (Table 1). In the jejunum, bursts of DCC's also occurred within several minutes in eight IBS patients (four diarrhoea, four constipation) but in only one control subject. Abdominal discomfort occurred at the time of multiple DCC's in all persons (Fig. 5).

*Luminal distension*

Pressures within the balloon at each volume of inflation were not significantly different between IBS and normal subjects (at 20 ml, 236 (9) *v* 220 (5) mmHg); pressures in persons experiencing pain were not different from those without pain. In the randomised balloon inflation (Fig. 6a), a pooled comparison for an effect of volume was significant ($p=0{\cdot}02$). Although a higher proportion of IBS patients than normal subjects experienced pain at the 15 ml and 20 ml volumes, this difference was of borderline statistical significance ($p=0{\cdot}08$). During graded inflation (Fig. 6b), a greater number of IBS than normal subjects experienced pain at volumes of 15, 17·5, and 20 ml. Comparisons at 15·0 and 17·5 ml between IBS and controls were of borderline significance ($p=0{\cdot}07$) and significant ($p=0{\cdot}03$), respectively. Differences at 20 ml were not significant.

## Discussion

Although all of the stimuli we applied have been used by others to unmask colorectal dysfunction in IBS,[5-13] they have not been previously applied to the small intestine in a systematic fashion. Patients with IBS responded to stimulation with exaggerated motor responses in the small bowel, and these were often accompanied by abdominal symptoms. CCK-OP produced the most marked differences between patients and controls, although the fatty meal also evoked greater motility and symptoms in IBS, and distension of the ileum provoked abdominal discomfort at lower volumes in IBS. Neostigmine stimulated motor activity in all regions, and did not evoke responses of different magnitudes in IBS and controls.

A second important finding was that, in some regards, IBS patients with predominant diarrhoea differed from those with predominant constipation. Those with diarrhoea were, in general, more sensitive to stimuli than were those with constipation. Altered bowel habits in patients with IBS cannot be specified absolutely, as many experience alternating patterns; nevertheless, this categorisation is well established.[4 12 16] Our classification into those with predominant diarrhoea or constipation was prospective, and was based on the past medical history, current symptoms, and responses to a standardised questionnaire.[20] All patients had abdominal pain as a major complaint; other clinical information has been reported elsewhere.[20]

Cholecystokinin has been implicated in the pathogenesis of IBS[5 6] because of its effects on smooth muscle of small and large intestine.[27 28] We stimulated with the octapeptide because it has all the activities of any form of CCK, is as potent as larger molecular forms, and it circulates in man.[29] We assessed its effects at doses[20 21] that ranged from subphysiological (minimal contraction of the gall bladder) to pharmacological (marked contraction of the gall bladder and abdominal side effects). Doses were evaluated by a simultaneous 'bioassay' of GB volume, as a well validated assay for circulating levels of the family of CCK peptides was not readily available. We also assayed CCK-OP at the point of infusion, as the peptide is known to adhere to containers, even in the presence of albumen, and so to be 'lost'. Further, variable losses between subjects made it necessary to analyse the results as individual dose response

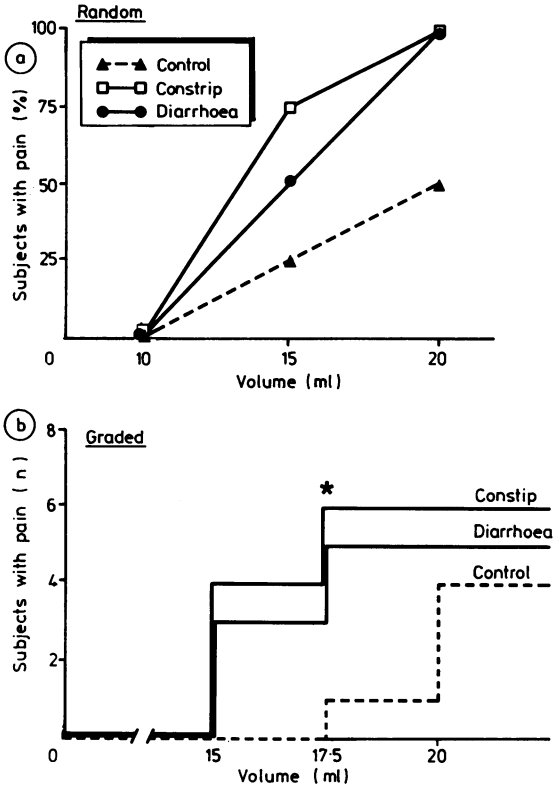


Fig. 6 *Response of the ileum to distension by a balloon. In Figure 6A, the mean percentage of patients experiencing pain after random distension of a balloon to volumes between 10 and 20 ml is shown. Constipation and diarrhoea refer to patients with irritable bowel syndrome. Figure 6B gives the results in studies in which the ileal volume of distension was increased step wise.*

relationships.[20 21] Motor responses of the small bowel to pharmacological (90% contraction of the GB) amounts were different among groups of subjects, though differences were impressive only at the jejunal level (Table 3). In earlier reports, the effects of CCK on the distal colon did not differ among subgroups of IBS,[5 6] but in the present study, the diarrhoea group showed a trend towards more sensitivity of the proximal colon to CCK-OP, when compared with IBS with constipation or controls. Earlier, we described that the sensitivity of the gall bladder to infused CCK-OP was also different among patients with IBS and controls.[20]

Qualitative and symptomatic responses to CCK-OP were also abnormal in IBS. Prolonged pressure waves were more frequently provoked in IBS patients than in controls, and these motor events were usually accompanied by episodes of cramping abdominal pain. Prolonged pressure waves, which are a propulsive in the canine ileum,[30] are a normal but infrequent feature of ileal motility in health.[22 23] Spontaneous, symptomatic PPC's were also more frequent in our IBS patients during prolonged periods of unstimulated (fasting) recordings.[18]

Patients with IBS had predictable responses overall to the meal, MMC's ceased and a 'fed pattern', equal in duration to that seen in controls, was established. In no group was there a systematic trend in RMI postprandially. This lead us to choose one point in the postprandial period at which to compare intestinal motility between groups. At the time of minimal gall bladder volume after the meal, RMI was not increased above basal levels in the normal group. Both groups of IBS patients, however, showed augmented motility, especially in the ileum and more so in those with diarrhoea. Although humoral and neural mechanisms other than CCK certainly participate in establishing a 'fed state' of motility, our high fat meal should have released CCK and the gall bladder was contracted at the time when intestinal motility was augmented in IBS. Thus, CCK probably contributed to the increased postprandial motility. Earlier, we were not able to show differences in the degree of gall bladder contraction between health and IBS in response to this meal.[20]

Neostigmine increased motility in all groups, with no obvious quantitative differences between IBS and controls. This drug, which appears to act by increasing acetylcholine at the smooth muscle membrane,[31] increases distal colonic motor activity in man,[29] excessively so in IBS.[9 10] Although the proximal colon is more sensitive to cholinergic agents than the distal colon,[32] effects on the human ileum have not been previously assessed. The provocation of PPC's by neostigmine in all groups suggests that cholinergic mechanisms contribute to their production. Discrete clustered contractions, were provoked by neostigmine more frequently in IBS than in controls, and this motor pattern was a feature of prolonged fasting recordings in these same patients.[18]

Distension of the ileum was the other stimulus to which patients with IBS were more sensitive; previous studies have shown these patients are more sensitive to colonic[11] and rectal[12] distension, although this may be caused by a low threshold for visceral pain or to an abnormal sensory perception. Determination of the sensitivity of the ileum to distension has not been previously assessed in IBS, although in an uncontrolled study, the distribution and referral of abdominal pain provoked by ileal distension was noted.[14]

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