

Functional Bowel Disorders



Recent Advances 13

A review of current literature by
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REVIEW

IBS BOOKLET

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Debate on appropriate sub-grouping of irritable bowel syndrome (IBS) patients continues with a recent study¹ suggesting that incorporation of psychosocial factors along with symptom and rectal sensory thresholds in cluster analyses identifies possibly more clinically meaningful sub-groups of IBS patients. Others have suggested that upper gastrointestinal (GI) symptoms suggestive of functional dyspepsia, and both lower abdominal pain and bloating are more frequent in constipation compared with diarrhoea predominant IBS², whilst the strongly held belief that IBS is more common in women than men may be more a reflection of consultation behaviour³. Another interesting case-report challenging current dogma comes from observations made on an IBS patient with concomitant, rapid cycling bipolar disorder. This individual actually experienced reduced IBS symptomatology at times of severe depression, suggesting that the symptoms of IBS and depression are not necessarily directly inter-related as some have previously suggested⁴.

Other noteworthy papers include: one showing that the selective serotonin reuptake inhibitor fluoxetine does not modify rectal sensory thresholds in either IBS patients with a hyper- or normally sensitive rectum, but that it may reduce abdominal pain in the hyper-sensitive patients⁵. Another suggests that rectal application of lidocaine may reduce both cutaneous and visceral hyperalgesia in patients with IBS⁶, an effect which can be mimicked by suggestions of pain relief⁷. In addition the belief that a meal has a high fat content, even if it does not, can induce symptoms of fullness and bloating in patients with functional dyspepsia, despite no change in gastric volume or plasma CCK concentrations⁸. Up to two thirds of patients with functional dyspepsia, especially ulcer-like dyspepsia, have significantly lower sensory thresholds than

controls and it has been claimed this figure can be increased to 95% by duodenal lipid infusion, raising the possibility of a potentially useful test for this condition⁹.

Increasing numbers of brain imaging studies are being reported in patients with functional gastrointestinal disorders. Trying to make sense of the results can be difficult because of differing techniques and protocols, as well as rather small numbers of patients in some series. For instance one study shows increased activity in the anterior cingulate cortex (ACC) with rectal distension in both healthy volunteers and IBS patients without a history of sexual or physical abuse but not in IBS patients with a history of abuse¹⁰. Another study shows increased insular cortex and prefrontal cortex, but not ACC, activity in IBS patients compared with controls¹¹. A further study found increased ACC activity in response to noxious visceral stimuli in IBS patients and to somatic stimuli in IBS patients presenting with concomitant fibromyalgia¹².

The investigation of the relationship of functional GI disorders to bacterial gastroenteritis has, until recently, been restricted to the development of IBS. A study investigating the prevalence of other functional GI disorders following infection has shown that IBS and functional diarrhoea, but not functional dyspepsia, are the most frequently reported conditions¹³. Other interesting observations in post infective IBS (PI-IBS) include a lower prevalence of psychiatric symptoms, as well as a predominance of diarrhoea associated with increased serotonin-containing enterochromaffin (EC) cells¹⁴. Anxiety, depression and fatigue also appear to be significantly increased in the PI IBS patients compared with those who were asymptomatic after infection¹⁵, but both groups have elevated lamina propria T lymphocytes compared with healthy controls^{15, 14}. Lamina propria T-lymphocyte but not EC counts decrease following treatment with prednisolone, but this did not appear to be associated with any symptomatic improvement in the PI IBS patients although it could be argued that the dose of prednisolone was not particularly



high¹⁶. Furthermore, mast cells numbers have been shown to be significantly increased in non-PI IBS patients compared with healthy controls^{17, 14}.

Finally, we include papers on: family practitioners attitudes and knowledge about IBS¹⁸, more evidence to suggest an increased prevalence of celiac disease in patients presenting with IBS¹⁹, high amplitude

propagated pressure waves in the colon²⁰, the relationship of unsuppressed post-prandial phasic contractility to functional dyspepsia²¹ and lastly, more evidence of familial clustering of IBS lending support to the concept that there may well be a genetic component to the pathophysiology of this condition^{22, 23}.



1. Cluster analysis of symptoms and health seeking behaviour differentiates subgroups of patients with severe irritable bowel syndrome.

Guthrie E; Creed F; Fernandes L; Ratcliffe J;
Van Der Jagt J; Martin J; Howlett S; Read N;
Barlow J; Thompson D; Tomenson B
Gut, 2003, 52 (11), 1616-22.

Condition which is diagnosed according to specific bowel symptom clusters. The aim of the present study was to identify subgroups of IBS subjects using measures of rectal sensitivity and psychological symptoms, in addition to bowel symptoms. Such groupings, which cross conventional diagnostic approaches, may provide greater understanding of the pathogenesis of the condition and its treatment. METHOD: A K means cluster analysis was used to group 107 clinic patients with IBS according to physiological, physical, and psychological parameters. All patients had severe IBS and had failed to respond to usual medical treatment. Twenty nine patients had diarrhoea predominant IBS, 26 constipation predominant, and 52 had an alternating bowel habit. RESULTS: The clusters were most clearly delineated by two variables: "rectal perceptual threshold (volume)" and "number of doctor visits". Three subgroups were formed. Group I comprised patients with low distension thresholds and high rates of psychiatric morbidity, doctor consultations, interpersonal problems, and sexual abuse. Group II also had low distension thresholds but low rates of childhood abuse and moderate levels of psychiatric disorders. Group III had high distension thresholds, constipation or alternating IBS, and low rates of medical consultations and sexual abuse. CONCLUSION: The marked differences across the three groups suggest that each may have a different pathogenesis and respond to different treatment approaches. Inclusion of psychosocial factors in the analysis enabled more clinically meaningful groups to be identified than those traditionally determined by bowel symptoms alone or rectal threshold.

2. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea.

Talley NJ; Dennis EH; Schettler-Duncan VA; Lacy BE;
Olden KW; Crowell MD
The American journal of gastroenterology, 2003,
98 (11), 2454-9.

OBJECTIVES: Distinguishing between irritable bowel syndrome (IBS) and functional dyspepsia can be challenging because of the variations in symptom patterns, which commonly overlap. However, the overlap is poorly quantified, and it is equally uncertain whether symptom patterns differ in subgroups of IBS arbitrarily defined by

primary bowel patterns of constipation (IBS-C) and diarrhea (IBS-D). We aimed to determine and to compare the distribution of GI symptoms, both, upper and lower, among IBS-C and IBS-D patients. METHODS: A total of 121 consecutive patients presenting with a diagnosis of IBS were grouped according to primary bowel symptoms as IBS-C (58 women and 18 men, mean age 47 +/- 17 yr) or IBS-D (26 women and 19 men, mean age 47 +/- 15 yr). The Hopkins Bowel Symptom Questionnaire, which includes a brief Quality of Life assessment, and the Hopkins Symptom Checklist 90-Revised were completed by all patients at intake. RESULTS: IBS-C patients reported significantly more overall GI symptoms when compared to patients with IBS-D (6.67 vs 4.62, respectively, $p < 0.001$). Abdominal pain patterns differed in patients with IBS-C versus IBS-D (lower abdominal pain: 40.8% vs 24.4% $p = 0.05$ and upper abdominal pain: 36.8% vs 24.4%, respectively). Bloating was substantially more common in IBS-C patients (75%) than in IBS-D (40.9%). There were no significant differences in personality subscales by IBS subgroup; however, somatization was positively associated with multiple symptom reports and was negatively correlated with quality of life. CONCLUSIONS: Upper GI symptoms consistent with functional dyspepsia were more frequent in IBS-C. Although there was considerable overlap of upper and lower GI symptoms in patients with IBS-C and IBS-D, the former had more frequent lower abdominal pain and bloating.

3. Current patterns of irritable bowel syndrome in Taiwan: The Rome II questionnaire on a Chinese population.

Lu C-L; Chen C-Y; Lang H-C; Luo J-C; Wang S-S;
Chang F-Y; Lee S-D
Alimentary Pharmacology and Therapeutics, 2003,
18 (11-12), 1159-1169.

Seen in Western countries. In Asia, however, it is less known and even less studied. Aim: To determine the prevalence and social impact of irritable bowel syndrome as well as the health-seeking behaviour of irritable bowel syndrome patients in Taiwan Methods: Using the modified Rome II questionnaire, a survey was carried out in a population receiving physical check-up ($n = 2865$). Results: The prevalence of irritable bowel syndrome in Taiwan was 22.1% and 17.5% ($kappa = 0.73$) according to the Rome II and I criteria, respectively. No gender difference was found between subjects with and without irritable bowel syndrome symptoms. Irritable bowel syndrome subjects were likely to undertake an excessive number of physician-visits ($P < 0.01$). Such subjects were often absent from work/school, with more days of absenteeism than irritable bowel syndrome-free subjects ($P < 0.01$). They also suffered obvious sleep disturbance ($P < 0.01$). Nearly half of the



irritable bowel syndrome subjects were 'consulters', and they were more likely to have frequent physician-visits, suffer from work/school absenteeism, and endure sleep disturbance and bowel symptoms than irritable bowel syndrome nonconsulters ($P < 0.05$). Conclusions: Irritable bowel syndrome is common in a Chinese population of Taiwan. Similar to irritable bowel syndrome in the West, it also involves significant social and medical burdens. However, in the irritable bowel syndrome subjects of Taiwan there is no gender difference, and more irritable bowel syndrome subjects will seek physician consultations, which may be due to Taiwan's easily accessible and affordable health care facilities.

4. Does depression influence symptom severity in irritable bowel syndrome? Case study of a patient with irritable bowel syndrome and bipolar disorder.

Crane C; Martin M; Johnston D; Goodwin GM
Psychosomatic Medicine, 2003, 65 (5), 919-923.

Objective: Irritable bowel syndrome (IBS) is frequently associated with mood disorder. However, it is typically difficult to distinguish between disturbed mood as a causal agent and disturbed mood as a consequence of the experience of IBS. This report considers the association between mood and symptom severity in a patient with diarrhea-predominant IBS and stable, rapid cycling bipolar disorder with a predominantly depressive course. Such a case provides an important opportunity to determine the direction of the relationship between mood and IBS symptom severity because the fluctuations of mood in bipolar disorder are assumed to be driven largely by biological, rather than psychosocial, processes. Methods: The study was carried out prospectively, with ratings of mood and IBS symptom severity made daily by the patient for a period of almost 12 months. Results: The patient experienced regular and substantial changes in mood as well as fluctuations in the level of IBS symptoms during the study period. Contrary to expectation, the correlation between mood and IBS symptom severity on the same day suggested that the patient experienced less severe IBS symptoms during periods of more severe depression. However, time series analysis revealed no significant association between these two processes when serial dependence within each series was controlled for. Conclusions: The unusual co-occurrence of IBS with bipolar disorder provides direct evidence to indicate that depression does not necessarily lead to an increase in the reported severity of IBS, at least in the context of bipolar disorder, and may under certain circumstances actually be associated with a reduction in the severity of IBS symptoms. Factors that might moderate the relationship between depression and symptom severity are discussed.

5. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: A double blind, randomized, placebo-controlled study.

Kuiken SD; Tytgat GNJ; Boeckxstaens GEE
Clinical Gastroenterology and Hepatology, 2003, 1 (3), 219-228.

Background & Aims: Although widely prescribed, the evidence for the use of antidepressants for the treatment of irritable bowel syndrome (IBS) is limited. In this study, we hypothesized that fluoxetine (Prozac), a selective serotonin reuptake inhibitor, has visceral analgesic properties, leading to increased sensory thresholds during rectal distention and improvement of symptoms, in particular in IBS patients with visceral hypersensitivity. Methods: Forty non-depressed IBS patients underwent a rectal barostat study to assess the sensitivity to rectal distention before and after 6 weeks of treatment with fluoxetine 20 mg or placebo. Abdominal pain scores, individual gastrointestinal symptoms, global symptom relief, and psychologic symptoms were assessed before and after the intervention. Results: At baseline, 21 of 40 patients showed hypersensitivity to rectal distention. Fluoxetine did not significantly alter the threshold for discomfort/pain relative to placebo, either in hypersensitive (19 ± 3 vs. 22 ± 2 mm Hg above MDP) or in normosensitive (34 ± 2 vs. 39 ± 4 mm Hg above MDP) IBS patients. Overall, 53% of fluoxetine-treated patients and 76% of placebo-treated patients reported significant abdominal pain scores after 6 weeks (not significant). In contrast, in hypersensitive patients only, fluoxetine significantly reduced the number of patients reporting significant abdominal pain. Gastrointestinal symptoms, global symptom relief, and psychologic symptoms were not altered. Conclusions: Fluoxetine does not change rectal sensitivity in IBS patients. Possible beneficial effects on pain perception need to be confirmed in larger trials.

6. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients.

Verne GN; Robinson ME; Vase L; Price DD
Pain, 2003, 105 (1-2), 223-230.

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal illnesses and is characterized by altered visceral perception. The aim of the study was to determine if local anesthetic blockade of peripheral visceral nociceptive input reduces both visceral and cutaneous secondary hyperalgesia in IBS patients. Ten women with IBS (mean age 30 ± 10 years) and ten control subjects (all women) (mean age 29 ± 7 years) rated pain intensity and unpleasantness to distension of the rectum (35 mmHg) and



thermal stimulation (47 degree C) of the foot before and after rectal administration of either lidocaine jelly or saline jelly in a double blind crossover design. Intrarectal lidocaine (300 mg) reduced reported rectal and cutaneous pain in all of the IBS patients. The effects were statistically much greater than those of placebo and most of the effects were present within 5-15 min after the onset of the treatment. In the control subjects, rectal lidocaine did not decrease pain report from visceral and cutaneous stimuli. The results of this study support the hypothesis that local anesthetic blockade of peripheral impulse input from the rectum/colon reduces both visceral and cutaneous secondary hyperalgesia in IBS patients. The results provide further evidence that visceral hyperalgesia and secondary cutaneous hyperalgesia in IBS reflects central sensitization mechanisms that are dynamically maintained by tonic impulse input from the rectum/colon. Rectal administration of lidocaine jelly may also be a safe and effective means of reducing pain symptoms in IBS patients.

7. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation.

Vase L; Robinson ME; Verne GN; Price DD
Pain, 2003, 105 (1-2), 17-25.

In order to investigate external factors that may influence the magnitude of placebo analgesia as well as psychological factors that mediate placebo analgesia, 13 irritable bowel syndrome (IBS) patients rated evoked rectal distension and cutaneous heat pain under the conditions of natural history (NH), rectal placebo (RP), rectal nocebo (RN), rectal lidocaine (RL) and oral lidocaine (OL). Patients were given verbal suggestions for pain relief and rated expected pain levels and desire for pain relief for both evoked visceral and cutaneous pain, respectively. Large reductions in pain intensity and pain unpleasantness ratings were found in the RP, RL and OL condition as compared to the natural history condition, whereas no significant difference in pain reduction between the three treatment conditions was found. Ratings during RN and NH were not statistically different. Compared to a previous study, which shows that rectal lidocaine reverses visceral and cutaneous hyperalgesia, these results suggest that adding a verbal suggestion for pain relief can increase the magnitude of placebo analgesia to that of an active agent. Since IBS patients rate these stimuli as much higher than do normal control subjects and since placebo effects were very large, they probably reflect anti-hyperalgesic mechanisms to a major extent. Expected pain levels and desire for pain relief accounted for large amounts of the variance in visceral pain intensity in the RP, RL, and OL condition (up to 81%), and for lower amounts of the variance in cutaneous pain

intensity. Hence, the combination of expected pain levels and desire for pain relief may offer an alternative means of assessing the contribution of placebo factors during analgesia.

8. Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia.

Feinle-Bisset C; Meier B; Fried M
Gut, 2003, 52 (10), 1414-8.

Pathophysiology of symptoms in functional dyspepsia (FD). In healthy subjects, cognitive factors enhance postprandial fullness; in FD patients, attention increases gut perception. We hypothesised that the information given to patients about the fat content of a meal would affect dyspeptic symptoms. **METHODS:** Fifteen FD patients were each studied on four occasions in a randomised double blind fashion. Over two days they ingested a high fat yoghurt (HF) and over the other two days a low fat yoghurt (LF). For each yoghurt, the patients received the correct information about its fat content on one day (HF-C, LF-C) and the opposite (wrong) information on the other day (HF-W, LF-W). Dyspeptic symptoms, plasma cholecystokinin (CCK) concentrations, and gastric volumes were evaluated. **RESULTS:** Both the fat content and information about the fat content affected fullness and bloating scores-both were higher after HF-C compared with LF-C, and LF-W compared with LF-C, with no differences between HF-C and HF-W. Nausea scores were higher after HF compared with LF, with no effect of the information about fat content. No differences between discomfort and pain scores were found between study conditions. Plasma CCK and gastric volumes were greater following HF compared with LF, with no effect of the information given to the patients. All differences are $p < 0.05$. **CONCLUSIONS:** Cognitive factors contribute to symptom induction in FD. Low fat foods may also elicit symptoms if patients perceive foods as high in fat, while CCK and gastric volumes do not appear to be affected by cognitive factors.

9. Effects of duodenal lipids on gastric sensitivity and relaxation in patients with ulcer-like and dysmotility-like dyspepsia.

Bjoernsson E; Sjoberg J; Ringstroem G; Norstroem M; Simren M; Abrahamsson H
Digestion, 2003, 67 (4), 209-17.

BACKGROUND/AIMS: Functional dyspepsia (FD) according to Rome II is divided into ulcer-like dyspepsia (ULD) and dysmotility-like dyspepsia (DLD). The rationale behind this is the assumption that the underlying pathophysiology is different, but this is largely unexplored. Our aim was to elucidate the differences in gastric sensorimotor function in



these subgroups of FD. 13 healthy controls (HC) and 20 patients with FD, 10 ULD and 10 DLD, were included. METHODS: A feeding tube was placed fluoroscopically in the proximal duodenum and a barostat balloon was placed in the proximal stomach. Sensory thresholds to gastric distention for first sensation, bloating and discomfort were assessed before and after duodenal lipid infusion (2 kcal/min, 60 min). RESULTS: Volume changes in the balloon were recorded as a measure of gastric tone. In FD patients, sensory thresholds in the fasting state were significantly lower than in HC, mostly due to gastric hypersensitivity in ULD. After lipid infusion, 95% of FD patients fell outside the normal range of HC for first sensation, bloating and/or discomfort, compared with 65% in the fasting state. Patients with ULD but not DLD had impaired fundic relaxation after duodenal lipids compared with HC. CONCLUSIONS: Investigating gastric sensorimotor function after duodenal lipid infusion, FD patients can accurately be differentiated from HC. Impaired fundic relaxation seems to be more common in patients with ULD.

10. Regional brain activation in response to rectal distension in patients with irritable bowel syndrome and the effect of a history of abuse.

Ringel Y; Drossman DA; Turkington TG; Bradshaw B; Hawk TC; Bangdiwala S; Coleman RE; Whitehead WE
Digestive Diseases and Sciences, 2003, 48 (9), 1774-1781.

Previous studies have demonstrated alterations in brain response to rectal distension in patients with irritable bowel syndrome (IBS) compared to controls. Our aim was to compare regional brain activity in response to rectal balloon distension in patients with IBS and healthy controls. We studied six patients with IBS and six healthy controls. Positron emission tomography scans were obtained during rectal balloon distensions. Statistical parametric mapping and region of interest analysis were performed to identify and compare differences in regional cerebral blood flow (CBF) for each distension pressure within and between the groups of interest. In post-hoc analyses, patients with a history of sexual or physical abuse were compared to patients without abuse. In response to rectal distension, controls exhibit a greater increase in anterior cingulate cortex (ACC) activity compared to the IBS group ($Z = 3.2$, $P = 0.001$). Thalamic activity was higher in the IBS patients relative to the control group ($Z = 3.3$, $P < 0.001$). Increased ACC activity was observed in IBS patients with no history of abuse ($Z = 5.2$, $P < 0.001$) similar to controls, whereas no such increased activity was noticed in the abused group. In conclusion, this study replicates previous findings showing alterations in brain response to rectal distension in patients with IBS. The observations on the effect of abuse suggest a possible modulating role of abuse history on this brain

response.

11. Functional brain imaging in irritable bowel syndrome with rectal balloon-distention by using fMRI.

Yuan YZ; Tao RJ; Xu B; Sun J; Chen KM; Miao F; Zhang ZW; Xu JY
World journal of gastroenterology: WJG, 2003, 9 (6), 1356-60.

AIM: Irritable bowel syndrome (IBS) is characterized by abdominal pain and changes in stool habits. Visceral hypersensitivity is a key factor in the pathophysiology of IBS. The aim of this study was to examine the effect of rectal balloon-distention stimulus by blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) in visceral pain center and to compare the distribution, extent, and intensity of activated areas between IBS patients and normal controls. METHODS: Twenty-six patients with IBS and eleven normal controls were tested for rectal sensation, and the subjective pain intensity at 90 ml and 120 ml rectal balloon-distention was reported by using Visual Analogue Scale. Then, BOLD-fMRI was performed at 30 ml, 60 ml, 90 ml, and 120 ml rectal balloon-distention in all subjects. RESULTS: Rectal distention stimulation increased the activity of anterior cingulate cortex (35/37), insular cortex (37/37), prefrontal cortex (37/37), and thalamus (35/37) in most cases. At 120 ml of rectal balloon-distention, the activation area and percentage change in MR signal intensity of the regions of interest (ROI) at IC, PFC, and THAL were significantly greater in patients with IBS than that in controls. Score of pain sensation at 90 ml and 120 ml rectal balloon-distention was significantly higher in patients with IBS than that in controls. CONCLUSION: Using fMRI, some patients with IBS can be detected having visceral hypersensitivity in response to painful rectal balloon-distention. fMRI is an objective brain imaging technique to measure the change in regional cerebral activation more precisely. In this study, IC and PFC of the IBS patients were the major loci of the CNS processing of visceral perception.

12. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia.

Chang L; Berman S; Mayer EA; Suyenobu B; Derbyshire S; Naliboff B; Vogt B; FitzGerald L; Mandelkern MA
American Journal of Gastroenterology, 2003, 98 (6), 1354-1361.

OBJECTIVE: Symptoms of irritable bowel syndrome (IBS) and fibromyalgia (FM) commonly coexist. We hypothesized that one of the mechanisms underlying this comorbidity is increased activation of brain regions concerned with the



processing and modulation of visceral and somatic afferent information, in particular subregions of the anterior cingulate cortex (ACC). METHODS: Regional cerebral blood flow (rCBF) was assessed in age-matched female IBS (n = 10) and IBS + FM (n = 10) subjects using ^{18}F -labeled positron emission tomography during noxious visceral (rectal) and somatic pressure stimuli. RESULTS: GI symptom severity was significantly higher in the IBS patients compared with the IBS + FM patients ($p < 0.05$). In addition, IBS + FM patients rated somatic pain as more intense than their abdominal pain ($p < 0.05$). Whereas the somatic stimulus was less unpleasant than the visceral stimulus for IBS patients without FM, the somatic and visceral stimuli were equally unpleasant in the IBS + FM group. Group differences in regional brain activation were entirely within the middle subregion of the ACC. There was a greater rCBF increase in response to noxious visceral stimuli in IBS patients and to somatic stimuli in IBS + FM patients. CONCLUSION: Chronic stimulus-specific enhancement of ACC responses to sensory stimuli in both syndromes may be associated with cognitive enhancement of either visceral (IBS) or somatic (IBS + FM) sensory input and may play a key pathophysiologic role in these chronic pain syndromes.

13. Does bacterial gastroenteritis predispose people to functional gastrointestinal disorders? A prospective, community-based, case-control study.

Parry SD; Stansfield R; Jelley D; Gregory W; Phillips E; Barton JR; Welfare MR

The American journal of gastroenterology, 2003, 98 (9), 1970-5.

OBJECTIVES: Irritable bowel syndrome (IBS) might develop after gastroenteritis. Most previous studies of this relationship have been uncontrolled, and little is known regarding other functional gastrointestinal disorders (FGIDs) after gastroenteritis. The primary aim of this study was to determine the frequency of IBS, functional dyspepsia, or functional diarrhea 6 months after bacterial gastroenteritis. METHODS: This was a prospective, community-based, case-control study. Cases had proven bacterial gastroenteritis, and controls were community-based. FGIDs were diagnosed with the use of self-completed Rome II modular questionnaires administered at baseline, 3, and 6 months. Subjects with prior FGIDs were excluded. The primary endpoint was the presence of one of the three specific FGIDs at 6 months. RESULTS: A total of 500 cases and 705 controls were identified. Of the 500 cases, 265 (53%) consented, but only 128 cases and 219 community controls who consented were eligible. At 6 months, 108 cases and 206 controls returned the questionnaire. FGIDs were

diagnosed in significantly more cases (n = 27, 25%) than controls (n = 6, 2.9%) (OR = 11.11, 95% CI = 4.42-27.92). IBS was diagnosed in 18 cases (16.7%) and four controls (1.9%) (OR = 10.1, 95% CI = 3.32-30.69); functional diarrhea in six cases (5.6%) and no controls. Functional dyspepsia was uncommon in both cases and controls. Similar findings were found at 3 months, with 29% of cases and 2.9% of controls having an FGID. CONCLUSIONS: Symptoms consistent with IBS and functional diarrhea occur more frequently in people after bacterial gastroenteritis compared with controls, even after careful exclusion of people with pre-existing FGIDs. The frequency is similar at 3 and 6 months. Our findings support the existence of postinfectious IBS and give an accurate estimate of its frequency.

14. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome.

Dunlop SP; Jenkins D; Spiller RC

American Journal of Gastroenterology, 2003, 98 (7), 1578-1583.

OBJECTIVE: Irritable bowel syndrome after gastroenteritis is well recognized. Our aim was to determine whether postinfective IBS (PI-IBS) has histological or clinical features that are distinct from those of IBS patients with no history of preceding infection. METHODS: A total of 75 consecutive IBS outpatients and 36 healthy control subjects completed a questionnaire detailing symptoms, mode of onset, and previous psychiatric history. All underwent a full diagnostic workup including rectal biopsy, which included immunostaining and quantification for lamina propria or intraepithelial T lymphocytes, serotonin-containing enterochromaffin (EC), and mast cells. Patients were divided according to onset of symptoms into PI-IBS (n = 23) or non-PI-IBS (n = 52) patients. RESULTS: Diarrhea predominance occurred more frequently in PI-IBS (70%) than in non-PI-IBS (42%) patients ($p = 0.03$). A history of previous treatment for anxiety or depression was present in 26% of PI-IBS patients compared to 54% of non-PI-IBS ($p = 0.02$). Biopsy results for all patients were normal using conventional criteria; however, quantification revealed that PI-IBS showed increased EC cells compared to those of non-PI-IBS patients ($p = 0.017$) and controls ($p = 0.02$). Lamina propria T lymphocytes were increased in PI-IBS ($p = 0.026$) and non-PI-IBS ($p = 0.011$) patients compared to controls. Mast cells were increased in non-PI-IBS patients ($p = 0.054$) compared to controls. CONCLUSIONS: Individuals with PI-IBS are a clinically distinct subgroup characterized by diarrheal symptoms, less psychiatric illness, and increased serotonin-containing EC cells compared to those with non-PI-IBS.



15. Relative Importance of Enterochromaffin Cell Hyperplasia, Anxiety, and Depression in Postinfectious IBS.

Dunlop SP; Jenkins D; Neal KR; Spiller RC
Gastroenterology, 2003, 125 (6), 1651-1659.

Background & Aims: Both psychological and mucosal changes (increased enterochromaffin [EC] cells and T lymphocytes) have been associated with postinfectious irritable bowel syndrome (PI-IBS). However, previous studies have been underpowered to determine the relative importance of these changes in predicting the development of PI-IBS. Our aim was to prospectively determine the relative importance of both psychological and histologic factors in the development of PI-IBS after *Campylobacter* infection. Methods: Questionnaires detailing psychological and bowel symptoms were sent to 1977 patients 3 months after infection. Twenty-eight patients with new-onset PI-IBS, 28 age- and sex-matched patient controls who were asymptomatic after infection, and 34 healthy volunteers underwent rectal biopsy, which was assessed for serotonin-containing EC cells, mast cells, and lamina propria T lymphocytes. Results: PI-IBS, predominantly of the diarrhea-predominant subtype, occurred in 103 of 747 (13.8%) of those infected. EC cell counts per high-power field (hpf) were higher in patients with PI-IBS (35.8 +- 1.2) compared with patient controls (30.6 +- 1.9; P = 0.022) and volunteers (29.1 +- 1.8; P = 0.006). Lamina propria T lymphocytes per hpf were higher in patients with PI-IBS (127.1 +- 8.7) and patient controls (113.4 +- 6.2) in contrast to healthy volunteers (97.1 +- 5.7) P = 0.006 and P = 0.058, respectively). Anxiety, depression, and fatigue were significantly increased in patients with PI-IBS compared with patient controls. Multivariate analysis indicated that increased EC cell counts and depression were equally important predictors of developing PI-IBS (relative risk, 3.8 and 3.2 for each standard deviation increase in respective values). Conclusions: Both increased EC cells and depression are important independent predictors of developing PI-IBS.

16. Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome.

Dunlop SP; Jenkins D; Neal KR; Naesdal J; Borgaonker M; Collins SM; Spiller RC
Alimentary Pharmacology and Therapeutics, 2003, 18 (1), 77-84.

Associated with increased serotonin-containing enterochromaffin cells and lymphocytes in rectal biopsies. Animal studies have suggested that steroids reduce the lymphocyte response and suppress some of the post-infectious changes in neuromuscular function. Aim: To

evaluate whether steroids reduce the number of enterochromaffin cells and improve the symptoms of post-infectious irritable bowel syndrome. Methods: Twenty-nine patients with post-infectious irritable bowel syndrome underwent a randomized, double-blind, placebo-controlled trial of 3 weeks of oral prednisolone, 30 mg/day. Mucosal enterochromaffin cells, T lymphocytes and mast cells were assessed in rectal biopsies before and after treatment, and bowel symptoms were recorded in a daily diary. Results: Initial enterochromaffin cell counts were increased and correlated with initial lamina propria T-lymphocyte counts (r = 0.460, P = 0.014). Enterochromaffin cell counts did not change significantly after either prednisolone (- 0.8% +- 9.2%) or placebo (7.9% +- 7.9%) (P = 0.5). Although lamina propria T-lymphocyte counts decreased significantly after prednisolone (22.0% +- 5.6%, P = 0.003), but not after placebo (11.5% +- 8.6%, P = 0.1), this was not associated with any significant treatment-related improvement in abdominal pain, diarrhoea, frequency or urgency. Conclusions: Prednisolone does not appear to reduce the number of enterochromaffin cells or cause an improvement in symptoms in post-infectious irritable bowel syndrome. Other approaches to this persistent condition are indicated.

17. Mast cells and neuropeptidergic terminals: Experimental studies of the mechanism of visceral hypersensitivity in irritable bowel syndrome.

Li ZS; Dong WZ; Zou DW; Zou XP; Xu GM; Zhu AY; Yin N; Gong YF; Sun ZX; Xu C; Man XH
Chinese Journal of Digestive Diseases, 2003, 4 (3), 111-117.

Objective: The failure of dysmotility to explain the symptoms of pain in irritable bowel syndrome (IBS) led to studies on visceral hypersensitivity. Mucosal mast cells (MC) may be one factor influencing the response of visceral afferents to mechanical and chemical stimuli because they are found in close proximity to gastrointestinal mucosal sensory nerve terminals containing neuropeptides and a bi-directional pathway linking the central nervous system, gut and MC has been demonstrated. Methods: The present study investigated the extent of MC and the neuropeptides, substance P (SP) and vasoactive intestinal peptide (VIP), in the intestinal mucosa of patients with IBS, as well as the location of the MC. The MC and neuropeptidergic terminals were stained histochemically and immunohistochemically, respectively, neuropeptide concentrations were measured by radioimmunoassay (RIA), and the results were investigated qualitatively and quantitatively by color image analyzer. The structural relation between the MC and neuropeptide terminals was studied by ultramicroscopy using in situ embedding technique. Results: In IBS, the number of MC in the terminal ileum, the ileocecal junction, and the ascending colon was significantly increased (P < 0.01), and



the MC had great variations in their extent and size. Significantly increased concentrations of VIP and SP were found in the colon of IBS patients compared with controls. A correlation between mucosal MC and the SP(VIP)-ergic terminals was found, and the MC were close to these terminals in the lamina propria, which demonstrated SP (VIP)-ergic terminals. Conclusions: Mast cells and the neuropeptides of intestinal mucosa may play a central role in gut hypersensitivity, resulting in both the motor response and visceral perceptions that occur with IBS.

18. Family practitioners' attitudes and knowledge about irritable bowel syndrome. Effect of a trial of physician education.

Longstreth GF; Burchette RJ
Family Practice, 2003, 20 (6), 670-674.

Background. Primary physicians care for most patients with irritable bowel syndrome (IBS), but data on their attitudes and knowledge about the disorder are limited to research in the UK. Objective. The purpose of the present study was to assess US family practitioners' attitudes and knowledge about IBS and determine the effect of a single education class on these measures. Methods. In a large health maintenance organization (HMO), a baseline group of family practitioners twice completed a questionnaire on attitudes and knowledge about IBS, 3 months apart. A class group completed it pre-class, immediately post-class and 3 months post-class. Result. Thirty-five physicians ranked IBS among five chronic, painful syndromes as highest in difficulty satisfying patients, tied with headache for highest in difficulty in practice strategy decision, second in time required, and fourth in diagnostic confidence and satisfaction in caring for patients. IBS and heartburn had widely separated rankings in all five attitudes. The correct answer rate on seven of 13 knowledge questions was <50%, and a majority did not identify the Rome II symptom criteria as typical and lacked other important knowledge. Of the 30 class physicians, the knowledge scores (mean +- SD; maximum possible, 13) of 29 increased from 5.59 +- 1.84 pre-class to 10.21 +- 1.76 immediately post-class ($P < 0.0001$); 3 months later, the scores were lower (8.93 +- 0.36) than post-class ($P < 0.0001$), but still higher than pre-class ($P < 0.0001$). Their attitude rankings were nearly identical pre-class and 3 months later ($P > 0.05$). In the 19 baseline physicians, IBS attitude rankings and knowledge scores did not change significantly over 3 months ($P > 0.05$). Conclusion. These US family practitioners had attitudes about IBS patients and lacked knowledge that could interfere with patient care. A single class improved short-term knowledge but had little effect on attitudes about IBS.

19. Coeliac disease presenting with symptoms of irritable bowel syndrome.

Shahbazkhani B; Forootan M; Merat S; Akbari MR; Nasserimoghadam S; Vahedi H; Malekzadeh R
Alimentary Pharmacology and Therapeutics, 2003, 18 (2), 231-235.

are parts of the criteria used for diagnosing irritable bowel syndrome. Aim: To find the frequency of coeliac disease among patients diagnosed as irritable bowel syndrome. Methods: During a period of one year, irritable bowel syndrome patients referred to a university clinic in Tehran were studied. For each patient, an asymptomatic sibling was enrolled as control. Serological tests for coeliac disease were performed in all patients and controls. If positive, duodenal biopsy was performed to confirm the diagnosis. Patients subsequently diagnosed as coeliac disease were placed on a gluten free diet and re-evaluated after 6 months. Results: One hundred and five cases of irritable bowel syndrome and 105 controls were enrolled. Coeliac disease was diagnosed in 12 of the irritable bowel syndrome patients and none of the controls. Eleven coeliac disease patients adhered to a gluten free diet. After 6 months, all 11 patients had significant improvement in symptoms and three were totally asymptomatic. Six allowed repeated endoscopy after 6 months of gluten free diet, of which five showed improvement in histological findings. Conclusions: Coeliac disease is a common finding among patients labelled as irritable bowel syndrome. In this sub-group, a gluten free diet may lead to a significant improvement in symptoms. Routine testing for coeliac disease may be indicated in all patients being evaluated for irritable bowel syndrome.

20. Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome.

Clemens CH; Samsom M; Roelofs JM; van Berge Henegouwen GP; Smout AJ
The American journal of gastroenterology, 2003, 98 (8), 1838-43.

OBJECTIVES: In the pathogenesis of irritable bowel syndrome (IBS), both increased visceral sensitivity and altered colonic motility seem to play a role. The aim of this study was to quantify the temporal relationship between pain episodes and the occurrence of high amplitude propagated pressure waves (HAPPWs).METHODS: A total of 11 IBS patients with the nonconstipation predominant pattern of IBS and 10 sex- and age-matched healthy volunteers were studied. On day 1, a solid state manometric catheter was positioned in the left colon and connected to a data logger. The subjects then went home. Thereafter they pressed a button on the data logger at the beginning and



end of each pain episode. The 24-h manometric signal recorded on day 2 was divided into consecutive 5-min periods. These periods were evaluated for the occurrence of pain and HAPPWs. Fisher's exact test was applied to calculate the probability that HAPPWs and pain episodes were unrelated. The symptom association probability (SAP) was calculated as $(1.0 - P) \times 100\%$. A SAP of $>95\%$ was considered to indicate that the observed association did not occur by chance. RESULTS: In four of seven patients with pain on day 2, the SAP was $>95\%$. HAPPWs that were related to pain originated at a more proximal level ($p = 0.026$) and occurred earlier ($p = 0.007$) than HAPPWs that were not related to pain. The duration of a pain period was correlated with the number of pain-related HAPPWs in that period ($r = 0.906$, $p = 0.013$). Two of the 10 healthy subjects experienced pain, and these pain episodes were not associated with HAPPWs. CONCLUSIONS: Using objective analysis techniques, an association between pain episodes and HAPPWs was found in nonconstipated IBS patients with pain. HAPPWs that are associated with pain are only slightly different from HAPPWs not associated with pain.

21. Unsuppressed postprandial phasic contractility in the proximal stomach in functional dyspepsia: relevance to symptoms.

Simren M; Vos R; Janssens J; Tack J
The American journal of gastroenterology, 2003, 98 (10), 2169-75.

OBJECTIVES: Phasic fundic contractions induce transient increases in gastric wall tension and can be perceived in patients with functional dyspepsia. It is unclear whether phasic contractile activity contributes to postprandial symptoms. The aim of the study was to examine postprandial phasic contractility in functional dyspepsia in relation to pathophysiological, clinical, and demographic variables. METHODS: A gastric barostat study was performed in 180 patients with functional dyspepsia and in 53 healthy control subjects. Sensitivity to distensions and the motor response to a standardized liquid meal were assessed. Phasic contractility in the proximal stomach was quantified using a motility index during three 30-min periods, namely, the preprandial period and the first and second postprandial periods. Unsuppressed phasic contractility after the meal was defined as motility index greater than mean + 2 SD in control subjects in at least one of the two postprandial periods. Relationships between unsuppressed phasic contractility and impaired accommodation, hypersensitivity, delayed gastric emptying, Helicobacter pylori (H. pylori) infection, symptom severity,

and demographic factors were assessed. RESULTS: Patients demonstrated a higher motility index than did control subjects during the first (22.8 ± 10.1 vs 20.3 ± 6.8 ml/s; $p = 0.04$) but not the second (19.9 ± 9.1 vs 18.7 ± 6.9 ml/s; ns) postprandial 30-min period. The motility index before the meal was similar in patients and controls. Unsuppressed phasic contractility postprandially was observed in 15% of the patients. H. pylori infection ($p = 0.01$), relevant or severe bloating ($p = 0.004$), and absence of nausea ($p = 0.004$) were found to be independently associated with unsuppressed phasic contractility after a meal. CONCLUSIONS: Unsuppressed postprandial phasic contractility in the proximal stomach is present in a small subset of patients with functional dyspepsia. It is associated with relevant and severe bloating and H. pylori infection but also with the absence of nausea.

22. Familial aggregation of irritable bowel syndrome: A prospective study.

Kalantar JS; Locke III GR; Zinsmeister AR; Beighley CM; Talley NJ
Gut, 2003, 52 (12), 1703-1707.

Report family members with similar symptoms, but family studies are lacking. We hypothesised that if there is familial aggregation, there would be an increased frequency of IBS in first degree relatives of IBS patients compared with relatives of controls (the patient's spouse). Methods: A valid self report bowel disease questionnaire (BDQ) that recorded symptoms, the somatic symptom checklist (a measure of somatisation), and a family information form (FIF) to collect the names and addresses of all first degree relatives were mailed to two groups of patients and their spouses (patients attending an IBS educational programme and residents of Olmsted County, Minnesota, who had been coded as IBS on a database). A BDQ was then mailed to all first degree relatives of subjects identified from the FIF. IBS diagnosis in the relatives was based on the Manning criteria. Results: The BDQ was sent to a total of 355 eligible relatives; 71% responded (73% relatives of patients, 67% relatives of spouses). Relatives were comparable in mean age, sex distribution, and somatisation score. IBS prevalence was 17% in patients' relatives versus 7% in spouses' relatives (odds ratio adjusted for age and sex 2.7 (95% confidence interval (CI) 1.2, 6.3)). When also adjusted for somatisation score, the odds ratio was reduced to 2.5 (95% CI 0.9, 6.7). Conclusions: Familial aggregation of IBS occurs, supporting a genetic or intrafamilial environment component, but this may be explained in part by familial aggregation of somatisation.



23. Is irritable bowel syndrome more likely to be persistent in those with relatives who suffer from gastrointestinal symptoms? A population-based study at three time points.

Kalantar JS; Locke III GR; Talley NJ; Zinsmeister AR; Fett SL; Melton III LJ
Alimentary Pharmacology and Therapeutics, 2003,
17 (11), 1389-1397.

Relatives who suffered from abdominal pain or bowel dysfunction would be at an increased risk of more persistent irritable bowel syndrome. Methods: A valid, self-report questionnaire was mailed to an age- and gender-stratified random sample of residents, aged 30-64 years, in Olmsted County, MN, USA, on three occasions over a 4-year period. Persistent irritable bowel syndrome was defined as the presence of irritable bowel syndrome on at least two of the three surveys, and fluctuating irritable bowel syndrome was defined as the presence of irritable bowel syndrome on only one of the surveys. Results: Subjects were less likely to have persistent irritable bowel syndrome over the age of 50 years [odds ratio (OR), 0.20; 95% confidence interval (CI), 0.09, 0.47]. A positive family history was reported by 23%. A family history of gastrointestinal symptoms was independently associated with persistent irritable bowel syndrome (vs. no irritable bowel syndrome: OR, 2.5; 95% CI, 1.3, 4.9) and fluctuating irritable bowel syndrome (vs. no irritable bowel syndrome: OR, 2.4; 95% CI, 1.3, 4.4). However, subjects reporting a positive family history were not more likely to report persistent vs. fluctuating irritable bowel syndrome (OR, 1.2; 95% CI, 0.5, 2.9). The use of non-steroidal anti-inflammatory drugs (OR, 2.3; 95% CI, 1.2, 4.3) and a history of food sensitivity (OR, 3.6; 95% CI, 1.9, 6.9) were the only other predictors of persistent irritable bowel syndrome. Conclusions: A history of abdominal pain or bowel troubles in first-degree relatives appears to be independently associated with both persistent and fluctuating irritable bowel syndrome.