

# Functional Bowel Disorders



Recent Advances 15

A review of current literature by  
L. A. Houghton and P. J. Whorwell



## Review of abstracts

This issue of our biannual review of functional gastrointestinal disorders reveals continued effort by researchers to develop and further explore many of the topics already discussed in previous issues. The scarcity of completely new lines of investigation is probably to be expected given the difficulties encountered when trying to define these conditions<sup>1,2</sup> and overlap between them, especially functional dyspepsia (FD) and irritable bowel syndrome (IBS)<sup>3</sup>. Recent studies have confirmed the role of gastroenteritis in IBS<sup>4,5</sup> as well as suggesting that the patient's socioeconomic environment as a child, as reflected in their level of affluence<sup>6</sup> and a parental history of bowel problems<sup>4</sup> may also be independent risk factors for the development of the condition. Psychopathology is commonly reported among treatment seeking patients with IBS, and some, but not all studies suggest abuse is also more common. Those individuals who do report abuse appear to be more at risk for substance abuse, dysthymia and generalized anxiety disorder<sup>7</sup>. Patients with IBS continue to be subjected to an excess of surgery which is probably inappropriate in many instances. Cholecystectomy, appendectomy, hysterectomy might be anticipated but there is also a worryingly high prevalence of back surgery<sup>8</sup>.

Interest in the role of inflammatory processes in IBS continues, with the demonstration in ileal and rectosigmoid biopsy specimens of increased density of neurone specific enolase, substance P, and 5-HT positively stained nerve fibres clustering around an increased number of mast cells<sup>5</sup> as well as elevated expression of IL-1beta mRNA in post dysenteric subjects. However, another study was unable to confirm this latter observation or other evidence of

inflammation although it did find elevated plasma concentrations of vasoactive intestinal peptide (VIP) which was unrelated to the bowel habit sub-type<sup>9</sup>. It has been suggested that dietary elimination, based on foods against which a patient has raised IgG antibodies, significantly improves the symptoms of IBS<sup>10</sup> and it is possible that such antibodies may also lead to an inflammatory process.

Hypersensitivity to acid has been the focus of more attention in relation to the pathogenesis of upper gastrointestinal functional disorders. In addition to previous evidence that sensitivity to exogenous acid may be a factor in FD, it has now been shown that, at least in a subset of patients, there is excess endogenous exposure to acid although this does not necessarily correlate with severity of symptoms<sup>11</sup>. It has also been suggested that the response of non cardiac chest pain to a high dose of a proton pump inhibitor may provide a sensitive diagnostic test for the reflux related variety of this condition<sup>12</sup>.

Patients with IBS commonly report an exacerbation of their symptoms with stress. This may be partly mediated by corticotrophin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH) release which is exaggerated in patients with IBS compared with healthy controls who seem to release more adrenalin and noradrenalin under stressful conditions<sup>13</sup>. It is therefore of interest, that the non-selective CRH receptor antagonist, alpha-helical CRH (alpha-hCRH), improves electrically stimulated rectal motility, visceral perception and negative mood in patients with IBS, without affecting the hypothalamo-pituitary-adrenal axis<sup>14</sup>. Thus CRF1 receptors may be a promising target for future pharmacological interventions in IBS.

Central processing of visceral stimuli continues to be explored in relation to IBS and allied conditions. For instance, unlike healthy volunteers who exhibit a



direct relationship between the intensity of a visceral stimulus and cortical activity volume, IBS patients show no such response<sup>15</sup>. In addition the endogenous pain inhibitory mechanisms appear to differ significantly between IBS patients and controls and also between subtypes of IBS<sup>16</sup>. Even at the level of the spinal cord nociceptive processing seems to differ between IBS and control subjects<sup>17</sup>.

Finally, we include papers on the continuing story of the link between colon ischemia and IBS<sup>18</sup>, the cost effectiveness of celiac sprue testing in IBS<sup>19</sup>, abnormal cardiovascular autonomic function in female IBS patients<sup>20</sup>, further evidence for a genetic link in IBS<sup>21</sup> and disordered sensory motor function in patients with functional dyspepsia<sup>22, 23</sup>.



### 1. Prevalence of irritable bowel syndrome (IBS) and variability of diagnostic criteria.

Bommelaer G, Poynard T, Le Pen C, Gaudin AF, Maurel F, Priol G, Amouretti M, Frexinos J, Ruszniewski P, El Hasnaoui A  
Gastroenterologie clinique et biologique, 2004, 28 (6-7 Pt 1), 554-61.

**OBJECTIVES:** The main objectives of this study were to assess whether the use of different definitions of irritable bowel syndrome (IBS) could influence measurements of its prevalence and characterize the patient population fulfilling these different diagnostic criteria. **METHOD:** A telephone survey was carried out by contacting 8,221 subjects aged  $\geq 18$  Years representative of the French population. A "screening" questionnaire based on three algorithms of IBS classification (Manning, with or without a notion of a minimal duration of symptoms, Rome I and Rome II) was used by specialised inquirers. **RESULTS:** Twenty three percent of the subjects interviewed stated that they had suffered from abdominal pain during the previous 12 Months. The prevalence of IBS considerably varied, depending on the diagnostic criteria used: 12% based on Manning criteria without reference to the duration of symptoms; 2.5% if the notion of duration of symptoms was added to the Manning criteria, and 2.1% and 1.1% based on the Rome I and Rome II criteria, respectively (the latter including the same notion of duration). In total, 212 subjects (2.6%) met at least one of the criteria including a minimal duration of symptoms, with a predominance for women (sex-ratio close to 2). **CONCLUSION:** The prevalence of IBS is strongly dependent on the classification algorithm employed. The requirement of a minimum duration of symptoms eliminates IBS in a large number of subjects complaining of abdominal disorders. Once these methodological variations were taken into account, the prevalence of IBS in France was found to be comparable to that published in international literature.

### 2. Subgroups of irritable bowel syndrome: A new approach

Walter SA, Skagerstroem E, Bodemar G  
European Journal of Gastroenterology and Hepatology, 2004, 16 (10), 991-994.

**OBJECTIVES:** The newly revised Rome criteria for the definition of irritable bowel syndrome (IBS), derived from the consensus of experts in the field, were developed in order to identify subgroups of IBS patients for research. The criteria have, to our knowledge, never been validated. Both when trying to include IBS patients in studies and in clinical practice we found it difficult to apply the Rome 2 supportive criteria. **Aim:** To study the variation of stool consistency and defecatory symptoms in IBS patients

prospectively with diary cards and to validate the Rome 2 supportive criteria. **Methods:** Sixty IBS patients, included by interview according to the Rome 1 criteria, recorded their bowel symptoms on diary cards over 40 days. Four subgroups were found, characterised by loose-stool-predominant, hard-stool-predominant, alternating stool consistency, and loose stools only. Urgency, straining and feeling of incomplete evacuation occurred in all but seven individuals, irrespective of subgroup. **Results:** The Rome 2 criteria could subclassify seven patients into diarrhoea-predominant IBS based on stool consistency and absence of straining and could subclassify no patients into constipation-predominant IBS, as urge was present in nearly all patients. Fifty-three patients could not be classified according to the Rome 2 criteria, as they had defecatory symptoms of all kinds. **Conclusion:** As the Rome 2 supportive criteria use the presence or absence of specific defecatory symptoms as an instrument for categorising IBS patients into diarrhoea- and constipation-predominant subgroups, these criteria could not be used for the majority of IBS patients in this study and should be reconsidered.

### 3. Impact of coexisting irritable bowel syndrome on symptoms and pathophysiological mechanisms in functional dyspepsia.

Corsetti M, Caenepeel P, Fischler B, Janssens J, Tack J  
The American journal of gastroenterology, 2004, 99 (6), 1152-9.

Epidemiological studies suggest considerable overlap between functional dyspepsia (FD) and irritable bowel syndrome (IBS). **AIM:** The aim of the present study was to investigate whether coexisting IBS is also associated with symptom pattern or pathophysiology in FD. **METHODS:** In 309 consecutive FD patients (207 women, age 42  $\pm$  0.8 yr), questionnaires were used to assess the dyspepsia symptom pattern and the Rome II criteria for IBS. The overall symptom severity was calculated adding the severity score (0-3, 0 = absent, 3 = severe) of eight dyspepsia symptoms. All patients underwent Helicobacter pylori testing, gastric barostat to determine sensitivity to distention and accommodation to a meal, and gastric emptying breath test. **RESULTS:** Fifty-four percent of the patients had FD alone, whereas 46% had FD + IBS. FD + IBS patients were more likely to be female (75% vs 60%,  $p < 0.01$ ) and to have a greater weight loss (5.4  $\pm$  0.6 vs 3.5  $\pm$  0.4 kg,  $p < 0.05$ ). Coexisting IBS did not increase the risk of having any of the dyspeptic symptoms but the overall symptom severity was significantly higher in FD + IBS (12.4  $\pm$  0.4 vs 9.8  $\pm$  0.3,  $p < 0.01$ ). FD + IBS patients had a lower threshold for first perception (2.9  $\pm$  0.3 vs 3.8  $\pm$  0.3 mmHg,  $p < 0.05$ ) and for discomfort (7.9  $\pm$  0.4 vs 9.5



+/- 0.5 mmHg,  $p < 0.05$ ) and a greater prevalence of hypersensitivity to gastric distention (44% vs 28%,  $p < 0.05$ ). Gastric emptying, accommodation to a meal, and prevalence of *H. pylori* infection did not differ in the two groups. **CONCLUSION:** About half of the FD patients fulfill the Rome II criteria for IBS. FD + IBS is more prevalent in female patients and is associated with a higher weight loss, with greater overall symptom severity, and with hypersensitivity to distention.

**4. Patients and nonconsulters with irritable bowel syndrome reporting a parental history of bowel problems have more impaired psychological distress.**

Kanazawa M, Endo Y, Whitehead WE, Kano M, Hongo M, Fukudo S

Digestive diseases and sciences, 2004, 49 (6), 1046-53.

Little is known about the prevalence and risk factors for development of irritable bowel syndrome (IBS) in Japan. In the United States, it is reported that heredity and social learning contribute to the development of IBS. Our aims were (1) to estimate the prevalence of IBS, (2) to confirm that subjects with IBS are more likely to have parents with a history of bowel problems, (3) to confirm that gastroenteritis is a risk factor for IBS, and (4) to determine whether these two risk factors interact with psychological distress. Prevalence was estimated from a sample of 417 young adults seen for annual health screening examinations. To evaluate risk factors related to consulting physicians, the 46 subjects who fulfilled Rome II diagnostic criteria for IBS but denied ever having seen a physician about these symptoms (IBS non-consulters) were compared to the 317 subjects who did not meet the criteria for IBS (controls) and to a group of 56 patients diagnosed with IBS by gastroenterologists (IBS patients). All subjects completed the Gastrointestinal Symptoms Rating Scale, the State-Trait Anxiety Inventory, the Self-Rating Depression Scale, the Perceived Stress Scale, and the SF-36 quality of life scale. Fourteen and two-tenths percent (15.5% of females and 12.9% of males) of the community sample met the criteria for IBS diagnosis, of whom 22% consulted physicians. IBS patients and IBS nonconsulters were more likely than controls to have a parental history (33.9 vs. 12.6%,  $P < 0.001$ , for patients and 26.1 vs. 12.6%,  $P < 0.01$ , for nonconsulters) and were more likely to report an infective history compared to controls (44.6 vs. 16.1%,  $P < 0.001$ , for patients and 32.6 vs. 16.1%,  $P < 0.01$ , for nonconsulters). Two-way analysis of variance showed that the parental history was associated with a significantly greater impact on symptoms of indigestion, diarrhea, constipation, state and trait anxiety, and the SF-36 scales for social functioning and role emotional and that an infective history was associated with a greater impact on bodily pain.

Both a parental history of bowel problems and a history of acute gastroenteritis are significant risk factors for development of IBS in Japan, as reported for the United States. Moreover, patients with such a family history show more psychological distress than other patients.

**5. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis.**

Wang LH, Fang XC, Pan GZ

Gut, 2004, 53 (8), 1096-101.

**BACKGROUND AND AIMS:** The incidence of irritable bowel syndrome (IBS) or functional bowel disorders (FBD) after bacillary dysentery (BD) has not been extensively evaluated, and little is known of the pathogenesis of post-infective (PI) IBS. Therefore, we investigated the incidence of IBS and FBD in a Chinese patient population who had recovered from BD. To further elucidate its pathogenesis, neuroimmunological changes, including interleukins (IL), mast cells, neuropeptides, and the relationship between mast cells and intestinal nerves, were investigated.

**METHODS:** A cohort study of 295 patients who had recovered from BD (shigella identified from stool in 71.4%) and 243 control subjects consisting of patient siblings or spouses who had not been infected with BD were included in the study. All subjects were followed up using questionnaires for 1-2 years to explore the incidence of FBD and IBS, as defined by the Rome II criteria. In 56 cases of IBS (PI and non-PI) from another source, the number of mast cells in biopsy specimens from the intestinal mucosa were stained with antitryptase antibody and counted under light microscopy. Also, the relationship of mast cells to neurone specific enolase (NSE), substance P (SP), 5-hydroxytryptamine (5-HT), or calcitonin gene related peptide positive nerve fibres was observed using double staining with alcian blue and neuropeptide antibodies. In 30 cases of IBS (PI-IBS,  $n = 15$ ) taken at random from the 56 cases, expression of interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , and IL-1 receptor antagonist (IL-1ra) mRNAs in intestinal mucosa were identified using reverse transcription-polymerase chain reaction. The above results were compared with 12 non-IBS controls. **RESULTS:** In the BD infected cohort, the incidences of FBD and IBS were 22.4% and 8.1% (in total)-10.2% (among those in who shigella were identified) respectively, which were significantly higher ( $p < 0.01$ ) than the incidences of FBD (7.4%) and IBS (0.8%) in the control cohort. A longer duration of diarrhoea ( $\geq 7$  days) was associated with a higher risk of developing FBD (odds ratio 3.49 [95% confidence interval 1.71-7.13]). Expression of IL-1 $\beta$  mRNA in terminal ileum and rectosigmoid mucosa was significantly higher in PI-IBS patients ( $p < 0.01$ ). The number of mast cells in the terminal ileum mucosa in PI-IBS (11.19 (2.83)) and non-PI-IBS patients (10.78 (1.23)) was



significantly increased compared with that (6.05 (0.51)) in control subjects ( $p < 0.01$ ). Also, in the terminal ileum and rectosigmoid mucosa of IBS patients, the density of NSE, SP, and 5-HT positively stained nerve fibres increased ( $p < 0.05$ ) and appeared in clusters, surrounding an increased number of mast cells ( $p < 0.01$  compared with controls). CONCLUSIONS: BD is a causative factor in PI-IBS. The immune and nervous system may both play important roles in the pathogenesis of PI-IBS.

#### 6. The irritable bowel syndrome has origins in the childhood socioeconomic environment.

Howell S, Talley NJ, Quine S, Poulton R  
The American journal of gastroenterology, 2004, 99 (8), 1572-8.

BACKGROUND: The childhood socioeconomic environment has been linked to adult health status in several studies. However, its role in the pathogenesis of adult irritable bowel syndrome (IBS) remains unknown. We aim to assess the influence of the childhood environment on adult IBS, using data from a New Zealand birth cohort study. METHODS: The Dunedin birth cohort was assembled in 1972-1973 and has been followed prospectively to age 26 ( $n = 980$ ). IBS was classified according to both Rome and Manning criteria, using self-reported symptom data obtained at age 26 yr. Childhood social class was used as a proxy measure of the quality of the childhood socioeconomic environment and was assigned according to the highest average socioeconomic (SES) level of either parent from interviews across the first 15 yr of life. RESULTS: Childhood social class was significantly associated with IBS according to Manning Criteria ( $p = 0.05$ ) and Rome II Criteria ( $p = 0.05$ ). The prevailing trend was identical for both measures of IBS in the sex-adjusted models: this trend can be characterized as a general, and near-linear decrease in the odds of IBS across decreasing levels of social class. Contrasts with the reference group were significant on all comparisons for Manning Criteria IBS (high vs upper middle,  $p = 0.04$ ; lower middle,  $p = 0.04$ ; low,  $p = 0.01$ ), and on comparisons involving the two lower social class groups for Rome II Criteria IBS (high vs lower middle,  $p = 0.03$ ; low,  $p = 0.03$ ). The associations were attenuated, but not eliminated by further adjustment for adult social class. CONCLUSIONS: An affluent childhood environment is an independent risk factor for adult IBS.

#### 7. The role of childhood abuse in Axis I and Axis II psychiatric disorders and medical disorders of unknown origin among irritable bowel syndrome patients.

Blanchard EB, Keefer L, Lackner JM, Galovski TE, Krasner S, Sykes MA  
Journal of psychosomatic research, 2004, 56 (4), 431-6.

OBJECTIVE: High rates of early abuse and psychopathology are commonly reported among treatment-seeking patients with irritable bowel syndrome (IBS). The purpose of this study is to further explore the relations among IBS, early abuse, Axes I and II psychopathology, and other medically unexplained disorders. METHODS: One hundred and ninety-six IBS patients seeking nondrug treatment for their symptoms were characterized in terms of their gastrointestinal (GI) status, psychiatric status (Axis I and Axis II), early abuse status, and the presence of other functional disorders. Patients were divided into two groups based on early abuse status. RESULTS AND CONCLUSION: No significant differences emerged between abused and nonabused groups on either the presence of Axis II disorders or other functional health conditions, although there were high levels of both in the IBS population. Patients with a history of abuse were significantly more likely to meet criteria for an Axis I disorder, especially substance abuse disorders, dysthymia, and generalized anxiety disorder.

#### 8. Irritable bowel syndrome and surgery: A multivariable analysis

Longstreth GF, Yao JF  
Gastroenterology, 2004, 126 (7), 1665-1673.

BACKGROUND AND AIMS: Patients with irritable bowel syndrome (IBS) have high surgical rates. We investigated the demographic and medical factors independently associated with surgical histories of health examinees. Methods: We applied multiple stepwise logistic regression analysis to self-completed questionnaire data from 89,008 examinees, assessing 6 surgeries as outcomes. We assessed questionnaire/physician record agreement of physician-diagnosed IBS and surgical history on 201 randomly selected examinees with (greater-than or equal to) 3 years of records. Results: Questionnaire/record agreement for IBS and surgery was 83.6% ( $\kappa = 0.68$ ) and 95.5%-100.0% ( $\kappa = 0.82-1$ ), respectively. IBS was reported by 4587 examinees (5.2%) (1382 men [3.0%] and 3205 women [7.5%]). Subjects with and without IBS, respectively, reported the following surgical procedures: cholecystectomy, 569 (12.4%) versus 3428 (4.1%),  $P < 0.0001$ ; appendectomy, 967 (21.1%) versus 9906 (11.7%),  $P < 0.0001$ ; hysterectomy, 1063 (33.2%) versus 6751 (17.0%),  $P < 0.0001$ ; back surgery, 201 (4.4%) versus 2436 (2.9%),  $P < 0.0001$ ; coronary artery surgery, 127 (2.8%) versus 2033 (2.4%),  $P > 0.05$ ; peptic ulcer surgery, 22 (0.5%) versus 277 (0.3%),  $P > 0.05$ . Among independent surgery associations, IBS was associated with cholecystectomy (adjusted odds ratio [OR], 2.09; 95% confidence interval [CI], 1.89-2.31;  $P < 0.0001$ ), appendectomy (OR, 1.45; 95% CI, 1.33-1.56;  $P < 0.0001$ ), hysterectomy (OR, 1.70; 95% CI, 1.55-1.87;  $P < 0.0001$ ), and back surgery (OR, 1.22; 95% CI, 1.05-1.43;



$P = 0.0084$ ). Conclusions: Health examinees with physician-diagnosed IBS report rates of cholecystectomy 3-fold higher, appendectomy and hysterectomy 2-fold higher, and back surgery 50% higher than examinees without IBS; IBS is independently associated with these surgical procedures.

**9. Elevated vasoactive intestinal peptide concentrations in patients with irritable bowel syndrome.**

Palsson OS, Morteau O, Bozyski EM, Woosley JT, Sartor RB, Davies MJ, Johnson DA, Turner MJ, Whitehead WE  
*Digestive diseases and sciences*, 2004, 49 (7-8), 1236-43.

The aim was to assess the roles of gut hormones and immune dysfunction in irritable bowel. In Study I, rectal mucosal samples examined blindly showed no histological evidence of inflammation in 16 irritable bowel patients compared to 17 healthy controls. The proinflammatory mediators interleukin-1beta and prostaglandin E2 also failed to show evidence of inflammation. Vasoactive intestinal peptide was elevated in irritable bowel ( $P = 0.01$ ), but substance P, calcitonin gene-related peptide, and somatostatin levels were similar to control values. In Study II, 30 irritable bowel patients had elevated ( $P = 0.002$ ) plasma concentrations of vasoactive intestinal peptide compared to 30 controls, and peptide levels were unrelated to whether the patient's predominant bowel habit was constipation, diarrhea, or both in alternation. In conclusion, no evidence of inflammation was detected in irritable bowel patients, but elevated vasoactive intestinal peptide concentrations were observed in both studies and might represent a potential diagnostic tool for irritable bowel syndrome.

**10. Food elimination based on IgG antibodies in irritable bowel syndrome: A randomised controlled trial**

Atkinson W, Sheldon TA, Shaath N, Whorwell PJ  
*Gut*, 2004, 53 (10), 1459-1464.

**BACKGROUND:** Patients with irritable bowel syndrome (IBS) often feel they have some form of dietary intolerance and frequently try exclusion diets. Tests attempting to predict food sensitivity in IBS have been disappointing but none has utilised IgG antibodies. **Aims:** To assess the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food. **Patients:** A total of 150 outpatients with IBS were randomised to receive, for three months, either a diet excluding all foods to which they had raised IgG antibodies (enzyme linked immunosorbant assay test) or a sham diet excluding the same number of foods but not those to which they had antibodies. **Methods:** Primary outcome measures were change in IBS symptom severity and global rating scores. Noncolonic symptomatology, quality of life, and anxiety/depression were secondary

outcomes. Intention to treat analysis was undertaken using a generalised linear model. **Results:** After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet (mean difference 39 (95% confidence intervals (CI) 5-72);  $p = 0.024$ ) with this value increasing to 26% in fully compliant patients (difference 98 (95% CI 52-144);  $p < 0.001$ ). Global rating also significantly improved in the true diet group as a whole ( $p = 0.048$ , NNT = 9) and even more in compliant patients ( $p = 0.006$ , NNT = 2.5). All other outcomes showed trends favouring the true diet. Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (difference 52 (95% CI 18-88);  $p = 0.003$ ). **Conclusion:** Food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.

**11. A pilot study on duodenal acid exposure and its relationship to symptoms in functional dyspepsia with prominent nausea.**

Lee KJ, Demarchi B, Demedts I, Sifrim D, Raeymaekers P, Tack J  
*The American journal of gastroenterology*, 2004, 99 (9), 1765-73.

**BACKGROUND:** Duodenal hypersensitivity to acid and decreased duodenal clearance of exogenous acid have been reported in functional dyspepsia (FD). However, the relevance of these abnormalities to spontaneous duodenal acid exposure and dyspeptic symptoms in FD is unknown. **AIMS:** To determine spontaneous duodenal acid exposure and its relationship with symptoms, duodenal sensitivity to acid, and the effects of a 5-HT(3) receptor antagonist on duodenal responses to acid in FD. **METHODS:** Eleven FD patients with prominent nausea and 11 healthy controls underwent 24-h ambulatory duodenal pH monitoring with assessment of dyspeptic symptoms. On the next day, duodenal bolus infusions of 5 ml of acid and normal saline were given in a randomized double-blind manner and repeated after ondansetron or a placebo. **RESULTS:** Nighttime duodenal acid exposure was similar, but FD patients had lower duodenal pH and higher duodenal % time ( $pH < 4$ ) than controls during the daytime and in the second postprandial 2 h ( $p < 0.05$ ). Seven patients (64%) with duodenal acid exposure above the normal range had higher severity scores for several dyspeptic symptoms including nausea. However, the symptom severity was poorly or weakly correlated to duodenal pH, and brief duodenal acid infusion did not affect any symptoms. Duodenal responses to exogenous acid were unaffected by 5-HT(3) receptor antagonism. **CONCLUSIONS:** Spontaneous duodenal acid exposure is increased in a subset of FD patients with prominent nausea, and this is associated with more severe dyspeptic symptoms. However, a direct



relationship between duodenal acid exposure and symptom severity is lacking.

**12. The effect of an empirical trial of high-dose lansoprazole on symptom response of patients with non-cardiac chest pain – a randomized, double-blind, placebo-controlled, crossover trial.**

Bautista J, Fullerton H, Briseno M, Cui H, Fass R  
Alimentary pharmacology & therapeutics, 2004,  
19 (10), 1123-30.

**BACKGROUND:** Empirical trial with high-dose omeprazole has been shown to be a sensitive tool for diagnosing patients with gastro-oesophageal reflux disease-related non-cardiac chest pain. **AIM:** To determine the clinical value of an empirical trial of high-dose lansoprazole in detecting patients with gastro-oesophageal reflux disease-related non-cardiac chest pain. **METHODS:** Patients who were referred by a cardiologist after a comprehensive evaluation, with at least three episodes per week of unexplained chest pain as the predominant symptom, were enrolled into the study. Oesophageal mucosal disease was determined by upper endoscopy followed by 24-h oesophageal pH monitoring to assess acid exposure. Patients were then randomized to either placebo or lansoprazole 60 mg am and 30 mg pm for 7 days. After a washout period of 1 week, patients crossed over to the other arm of the study for an additional 7 days. Patients completed a daily diary assessing severity and frequency of chest pain as the predominant symptom throughout the baseline treatment and washout periods. The lansoprazole empirical trial was considered diagnostic if chest pain score improved > or =50% than baseline. **RESULTS:** Of the 40 patients with non-cardiac chest pain that were enrolled, 18 (45%) had erosive oesophagitis and/or abnormal pH test (gastro-oesophageal reflux disease-positive) and 22 (55%) had both tests negative (gastro-oesophageal reflux disease-negative). Of the gastro-oesophageal reflux disease-positive patients, 14 (78%) had significantly higher symptom improvement on lansoprazole than on placebo (22%) ( $P = 0.0143$ ). Of the gastro-oesophageal reflux disease-negative group, two (9.1%) markedly improved on the medication and eight (36.3%) on placebo ( $P = 0.75$ ). The sensitivity and specificity of the lansoprazole empirical trial was 78 and 80%, respectively. By day 2, 12 (85.7%) of the gastro-oesophageal reflux disease-related non-cardiac chest pain responders had either complete or almost complete symptom resolution. **CONCLUSIONS:** The lansoprazole empirical trial is highly sensitive and specific for diagnosing gastro-oesophageal reflux disease-related non-cardiac chest pain patients. The trial enables diagnosing most of the responders within the first 2 days and thus a shorter

duration of therapy may be considered in a subset of non-cardiac chest pain patients.

**13. Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress.**

Posserud I, Agerforz P, Ekman R, Bjoernsson ES,  
Abrahamsson H, Simren M  
Gut, 2004, 53 (8), 1102-8.

**BACKGROUND AND AIMS:** Stress often worsens the symptoms of irritable bowel syndrome (IBS). We hypothesised that this might be explained by altered neuroendocrine and visceral sensory responses to stress in IBS patients. **SUBJECTS AND METHODS:** Eighteen IBS patients and 22 control subjects were assessed using rectal balloon distensions before, during, and after mental stress. Ten controls and nine patients were studied in supplementary sessions. Rectal sensitivity (thresholds and intensity-visual analogue scale (VAS)) and perceived stress and arousal (VAS) were determined. Plasma levels of corticotropin releasing factor (CRF), adrenocorticotrophic hormone (ACTH), cortisol, noradrenaline, and adrenaline were analysed at baseline, immediately after stress, and after the last distension. Heart rate was recorded continuously. **RESULTS:** Thresholds were increased during stress in control subjects ( $p < 0.01$ ) but not in IBS patients. Both groups showed lower thresholds after stress ( $p < 0.05$ ). Repeated distensions without stress did not affect thresholds. Both groups showed increased heart rate ( $p < 0.001$ ) and VAS ratings for stress and arousal ( $p < 0.05$ ) during stress. Patients demonstrated higher ratings for stress but lower for arousal than controls. Basal CRF levels were lower in patients ( $p < 0.05$ ) and increased significantly during stress in patients ( $p < 0.01$ ) but not in controls. Patients also responded with higher levels of ACTH during stress ( $p < 0.05$ ) and had higher basal levels of noradrenaline than controls ( $p < 0.01$ ). Controls, but not patients, showed increased levels of adrenaline and noradrenaline in response to stress ( $p < 0.05$ ). **CONCLUSIONS:** Stress induced exaggeration of the neuroendocrine response and visceral perceptual alterations during and after stress may explain some of the stress related gastrointestinal symptoms in IBS.

**14. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome.**

Sagami Y, Shimada Y, Tayama J, Nomura T, Satake M, Endo Y, Shoji T, Karahashi K, Hongo M, Fukudo S  
Gut, 2004, 53 (7), 958-64.

**BACKGROUND AND AIMS:** Corticotropin releasing hormone (CRH) is a major mediator of the stress response in the



brain-gut axis. Irritable bowel syndrome (IBS) is presumed to be a disorder of the brain-gut link associated with an exaggerated response to stress. We hypothesised that peripheral administration of alpha-helical CRH (alphahCRH), a non-selective CRH receptor antagonist, would improve gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation in IBS patients. METHODS: Ten normal healthy subjects and 10 IBS patients, diagnosed according to the Rome II criteria, were studied. The tone of the descending colon and intraluminal pressure of the sigmoid colon were measured at baseline, during rectal electrical stimulation (ES), and at recovery after administration of saline. Visceral perception after colonic distension or rectal ES was evaluated as threshold values on an ordinate scale. The same measurements were repeated after administration of alphahCRH (10 micro g/kg). RESULTS: ES induced significantly higher motility indices of the colon in IBS patients compared with controls. This response was significantly suppressed in IBS patients but not in controls after administration of alphahCRH. Administration of alphahCRH induced a significant increase in the barostat bag volume of controls but not in that of IBS patients. alphahCRH significantly reduced the ordinate scale of abdominal pain and anxiety evoked by ES in IBS patients. Plasma adrenocorticotrophic hormone and serum cortisol levels were generally not suppressed by alphahCRH. CONCLUSION: Peripheral administration of alphahCRH improves gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation, without affecting the hypothalamo-pituitary-adrenal axis in IBS patients.

**15. Absence of increasing cortical fMRI activity volume in response to increasing visceral stimulation in IBS patients.**

Sidhu H, Kern M, Shaker R  
American journal of physiology. Gastrointestinal and liver physiology, 2004, 287 (2), G425-35.

Cerebral cortical activity associated with perceived visceral sensation represents registration of afferent transduction and cognitive processes related to perception. Abnormalities of gut sensory function can involve either or both of these processes. Cortical registration of subliminal viscerosensory signals represents cerebral cortical activity induced by stimulation of intestinal sensory neurocircuitry without the influence of perception-related cortical activity, whereas those associated with perception represent both neural circuitry and cognitive processes. Our aims were to determine and compare quantitatively cerebral cortical functional magnetic resonance imaging (fMRI) activity in response to subliminal, liminal, and nonpainful supraliminal rectal distension between a group of irritable bowel

syndrome (IBS) patients and age/gender-matched controls. Eight female IBS patients and eight age-matched healthy female control subjects were studied using brain fMRI techniques. Three barostat-controlled distension levels were tested: 1) 10 mmHg below perception (subliminal), 2) at perception (liminal), and 3) 10 mmHg above perception (supraliminal). In control subjects, there was a direct relationship between stimulus intensity and cortical activity volumes, ie., the volume of fMRI cortical activity in response to subliminal (3,226 +/- 335 microl), liminal (5,751 +/- 396 microl), and supraliminal nonpainful stimulation (8,246 +/- 624 microl) were significantly different ( $P < 0.05$ ). In contrast, in IBS patients this relationship was absent and fMRI activity volumes for subliminal (2,985 +/- 332 microl), liminal (2,457 +/- 342 microl), and supraliminal nonpainful stimulation (2,493 +/- 351 microl) were similar. Additional recruitment of cortical fMRI activity volume in response to increasing stimulation from subliminal to liminal and supraliminal domains is absent in IBS patients, suggesting a difference in the processing of perceived stimulation compared with controls.

**16. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls**

Wilder-Smith CH, Schindler D, Lovblad K, Redmond SM, Nirkko A  
Gut, 2004, 53 (11), 1595-1601.

BACKGROUND AND AIMS: Many patients with irritable bowel syndrome (IBS) show intestinal hypersensitivity to distension and sensitisation after repeated intestinal distensions. Abnormalities in endogenous pain inhibitory mechanisms, such as diffuse noxious inhibitory controls (DNIC), may be implicated and were investigated during brain functional magnetic resonance imaging (fMRI). Patients and methods: fMRI was performed in 10 female patients with IBS (five constipated (IBS-C) and five with diarrhoea (IBS-D)) and 10 female healthy controls during rectal balloon distension alone or during activation of DNIC by painful heterotopic stimulation of the foot with ice water. Rectal pain was scored with and without heterotopic stimulation (0 = none, 10 = maximal). Results: Heterotopic stimulation decreased median rectal pain scores significantly in healthy controls (-1.5 (interquartile range -2 to -1);  $p = 0.001$ ) but not in IBS-C (-0.7 (-1 to 0.5)), IBS-D (-0.5 (-1.5 to 0.5)), or in all IBS patients (0 (-1.5 to 1.3)). Brain activation changes during heterotopic stimulation differed highly significantly between IBS-C, IBS-D, and controls. The main centres affected were the amygdala, anterior cingulate cortex, hippocampus, insula, periaqueductal gray, and prefrontal cortex, which form part



of the matrix controlling emotional, autonomic, and descending modulatory responses to pain. Conclusions: IBS-C and IBS-D appear to have differing abnormal endogenous pain inhibitory mechanisms, involving DNIC and other supraspinal modulatory pathways.

**17. Alteration of the spinal modulation of nociceptive processing in patients with irritable bowel syndrome**

Coffin B, Bouhassira D, Sabate J-M, Barbe L, Jian R Gut, 2004, 53 (10), 1465-1470.

**BACKGROUND:** Visceral hypersensitivity has been evidenced in patients with irritable bowel syndrome (IBS) but its mechanisms remain poorly elucidated. We investigated the spinal transmission of nociceptive signals in IBS patients by analysing the effects of rectal distensions on electromyographic recordings of the somatic nociceptive flexion (RIII) reflex, an objective index of spinal nociceptive processes. **Methods:** Fourteen IBS and 10 healthy volunteers were included in the study. Slow ramp (40 ml/min) and rapid phasic (900 ml/min, 10, 20, 30, and 40 mm Hg) rectal distensions were randomly performed while the RIII reflex evoked by electrical stimulation of the sural nerve at the ankle was continuously recorded from the ipsilateral biceps femoris. **Results:** In healthy volunteers, significant progressive inhibition of the RIII reflex was observed during slow ramp distension (61 (13)% of control values) while biphasic effects (facilitation and inhibition) were observed during rapid distensions. In contrast, in IBS patients, the RIII reflex was significantly facilitated during slow ramp distension (139 (15)% of control values) and inhibitions induced by rapid distensions were significantly reduced. Volumes of distension and rectal compliance were similar in both groups. **Conclusions:** Our results provide direct evidence that a hyperexcitability of spinal nociceptive processes is present in a large subgroup of IBS patients.

**18. Risk factors for colon ischemia.**

Walker AM, Bohn RL, Cali C, Cook SF, Ajene AN, Sands BE The American journal of gastroenterology, 2004, 99 (7), 1333-7.

**BACKGROUND:** To identify predictors of colon ischemia, we examined demographic and clinical characteristics of patients, as well as their prior health care utilization. **METHODS:** Using insurance data, we identified 700 persons at least 20-yr old with presumed colon ischemia between 1995 and 1999, and 6,440 controls. Case identification was based on diagnosis and procedure codes in insurance claims for which we used a previously reported, validated algorithm. We ascertained preceding medical diagnoses and the use of drugs and health services from the insurance claims files. **RESULTS:** Patients with colon ischemia were

nearly three times as likely to have IBS than controls. A history of nonspecific colitis, lower gastrointestinal tract hemorrhage, systemic rheumatologic disorders, and ischemic heart disease in the preceding 6 months, and abdominal surgery in the past month were also much more common in colon ischemia cases than controls. Use of a drug to treat diarrhea was strongly associated with risk. The most prevalent risk factor for colon ischemia was the use of drugs with a side effect of constipation, found in one-third of cases and one in nine controls. Cases had seen physicians, particularly gastroenterologists, much more commonly in the preceding 6 months than had controls. **CONCLUSIONS:** Clinically evident colon ischemia arises preferentially in persons with prior abdominal complaints, many of whom carry a diagnosis of IBS. Drugs that reduce bowel motility may constitute a widespread and potentially avoidable risk factor. The frequency of preceding doctor visits, without a specific diagnosis, suggests that colon ischemia may have a prolonged subacute presentation.

**19. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis.**

Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS Gastroenterology, 2004, 126 (7), 1721-32.

**BACKGROUND & AIMS:** Some patients with diarrhea-predominant irritable bowel syndrome (IBS-D) may have undiagnosed celiac sprue (CS). Because the symptoms of CS respond to a gluten-free diet, testing for CS in IBS may prevent years of morbidity and attendant expense. We sought to determine whether this might be a cost-effective diagnostic strategy in IBS-D. **METHODS:** We used decision analysis to calculate the cost-effectiveness of 2 competing strategies in IBS-D: (1) start empirical IBS treatment and (2) perform serologic test for CS followed by endoscopic biopsy for positive tests. The base-case cohort had a CS prevalence of 3.4%, which was varied between 0% and 100% in sensitivity analysis. The outcome measure was cost per symptomatic improvement. **RESULTS:** Under base-case conditions, testing for CS instead of starting empiric IBS therapy cost an incremental \$11,000 to achieve one additional symptomatic improvement. Testing for CS became the dominant strategy when the prevalence of CS exceeded 8%, the specificity of CS testing exceeded 98%, or the cost of IBS therapy exceeded \$130/month. The incremental cost-effectiveness of testing for CS exceeded \$50,000 when the prevalence fell below 1%. **CONCLUSIONS:** Testing for CS in patients with IBS-D has an acceptable cost when the prevalence of CS is above 1% and is the dominant strategy when the prevalence exceeds 8%. The decision to test should be based on a consideration of the population prevalence of underlying CS, the operating characteristics



of the screening test employed, and the cost of proposed therapy for IBS.

**20. Autonomic cardiovascular responses are impaired in women with irritable bowel syndrome**

Waring WS, Chui M, Japp A, Nicol EF, Ford MJ  
Journal of Clinical Gastroenterology, 2004, 38 (8), 658-663.

GOALS: This study characterizes cardiovascular autonomic function in women with irritable bowel syndrome (IBS), using standardized techniques. BACKGROUND: Autonomic dysfunction is believed to contribute to abnormal gastrointestinal motility and visceral hypersensitivity in IBS. There is mounting evidence of generalized impairment of autonomic activity in patients with IBS. Study: Thirty women aged 39 years (95% C.I. 25-53 years) diagnosed with IBS, and 30 age-matched healthy women were studied. The ratio of low frequency to high frequency heart rate variability domains (LF:HF ratio) was used to represent cardiac sympathovagal activity, and orthostatic testing and sustained isometric handgrip exercise were used as sympathetic stimuli. Parasympathetic activity was represented by the expiratory to inspiratory R-R interval (E:I) ratio during deep breathing at 6 minutes(sup(-1)). Results: LF:HF responses to handgrip exercise (316%, C.I. 134% to 498% vs. 107%, C.I. 15% to 153%;  $P < 0.05$ ) and orthostatic testing (648%, C.I. 520% to 904% vs. 330%, C.I. 140% to 520%;  $P < 0.05$ ) were higher in IBS patients than controls, and the E:I ratio was significantly lower (1.47, C.I. 1.33-1.61 vs. 1.20, C.I. 1.14-1.26;  $P < 0.01$ ). Conclusions: Autonomic cardiovascular function is impaired in IBS, manifest as attenuated cardio-vagal tone, and relative sympathetic excess during stimulated conditions.

**21. Association of the -1438 G/A and 102 T/C polymorphism of the 5-HT<sub>2A</sub> receptor gene with irritable bowel syndrome 5-HT<sub>2A</sub> gene polymorphism in irritable bowel syndrome**

Pata C, Erdal E, Yazici K, Camdeviren H, Oezkaya M, Ulu O  
Journal of Clinical Gastroenterology, 2004, 38 (7), 561-566.

GOALS: The aim of this study is to investigate whether there were any association between the 102 T/C and -1438 G/A polymorphisms of the 5-HT<sub>2A</sub> receptor gene and IBS, and abdominal pain, anxiety and depression. BACKGROUND: Genes involved in serotonin (5-HT) metabolism are good candidates for the pathogenesis of irritable bowel syndrome (IBS). Recently, a silent polymorphism in the 5-HT<sub>2A</sub> receptor gene was identified that is defined by a T to C transition at position 102. Also, a novel G to A base change at position -1438 of the promoter region has been detected in 5-HT<sub>2A</sub> receptor gene. Study: Fifty-four patients with IBS diagnosed according to the Rome 1 criteria and 107 healthy

individuals were included in the study. PCR was used to amplify a 468-bp (G(rightwards arrow)A) and 342-bp (T(rightwards arrow)C) fragment of genomic DNA containing the polymorphism. Hospital anxiety and depression scale was used to assess the risk of depression and anxiety. Severity of chronic abdominal pain was determined by visual analogue scale (VAS). Results: It was shown that there was a high incidence of homozygote C allele of the 102T/C polymorphism (%22.2; OR: 7.89,  $P = 0.04$ ) and homozygote A allele of the -1438 G/A promoter region (%37; OR: 11.14,  $P = 0.01$ ) in patients with IBS. The risk of having an anxiety disorder was 83.3% in patients with C/C genotype, which was higher than other allele carrying patients, and overall mean (%52.7). ( $x^{(sup)2}$ ) = 8.56,  $P = 0.014$ ). The patients with T/T genotype had a VAS score of 54.93 +- 2.59 mm, which was significantly higher than that of the patients with other genotypes ( $\pi = 0.02$ ,  $p2 = 0.001$ ). Conclusion: This study suggests that the patients with homozygote C allele of the 102 T/C polymorphism of the 5-HT<sub>2A</sub> receptor gene, have a high risk of IBS. On the other hand, T/T genotype of 102 T/C polymorphism may be associated with more severe pain in patient with IBS.

**22. Role of tension receptors in dyspeptic patients with hypersensitivity to gastric distention.**

Tack J, Caenepeel P, Corsetti M, Janssens J  
Gastroenterology, 2004, 127 (4), 1058-66.

BACKGROUND & AIMS: Studies in health have shown that tension-sensitive mechanoreceptors mediate sensitivity to gastric distention. A role for these mechanoreceptors in perception or symptoms in hypersensitive functional dyspepsia (FD) has not been established. Tension-sensitive mechanoreceptors are activated during phasic contractions and inactivated during gastric relaxation. The aim of the present study was to investigate whether hypersensitive FD patients perceive spontaneous changes in fundic wall tension and whether fundus-relaxing drugs decrease sensitivity to gastric distention and meal-related symptoms. METHODS: Fifty patients were selected after a barostat study established gastric hypersensitivity. In 12 patients, an intragastric balloon was inflated with a fixed volume just below perception thresholds and patients were asked to indicate changes in perception on a keypad, and the relationship between perception and contractions was analyzed. In 20 patients, we studied the influence of the fundus-relaxing drug sumatriptan on sensitivity to gastric distention. In, respectively, 10 and 8 patients, we studied the influence of the fundus-relaxing drugs sumatriptan and clonidine on meal-related symptoms. RESULTS: The majority of patients had a statistically significant association between perception and phasic isovolumetric contractions.



Pretreatment with sumatriptan increased both pressures and volumes needed to induce first perception and discomfort.

Pretreatment with sumatriptan and clonidine both significantly decreased meal-induced symptoms.

**CONCLUSIONS:** Patients with hypersensitivity to gastric distention perceive isovolumetric phasic contractions of the proximal stomach. Fundus-relaxing drugs decrease sensitivity to gastric distention and decrease meal-induced symptoms in these patients. The findings are compatible with involvement of tension mechanoreceptors in symptom generation in hypersensitive FD.

**23. Symptom patterns in functional dyspepsia and irritable bowel syndrome: Relationship to disturbances in gastric emptying and response to a nutrient challenge in consulters and non-consulters**

Haag S, Talley NJ, Holtmann G

Gut, 2004, 53 (10), 1445-1451.

**BACKGROUND:** Our aim was to assess the relationship between gastric motor and sensory function and symptom patterns in community subjects and patients with functional dyspepsia (FD) or irritable bowel syndrome (IBS). **Methods:** We recruited 291 asymptomatic blood donors, 151 symptomatic blood donors (recurrent abdominal pain or discomfort), and 40 patients with FD or IBS. Abdominal

symptoms were assessed using the bowel disease questionnaire (BDQ) and, in addition, the most bothersome symptom complex identified (dysmotility-type, ulcer-type dyspepsia, or IBS). Gastric emptying time (GET ( $t_{(1/2)}$ ), min) was measured by ( $^{13}$ C)-octanoic breath test and a nutrient challenge performed. Twenty randomly selected asymptomatic blood donors, 48 symptomatic blood donors (30 FD, 18 IBS), and 40 patients (23 FD, 17 IBS) had additional function testing. Results: GET ( $t_{(1/2)}$ ) was significantly ( $p < 0.05$ ) longer in blood donors with FD symptoms (99 (6) min) and FD patients (110(12) min) compared with asymptomatic controls (76.7(7) min), but was not significant in IBS blood donors or patients. Overall, 25 of 48 blood donors with symptoms and 18 of 40 patients had slow gastric emptying. GET was most delayed in subjects with predominantly dysmotility-type symptoms (167(36) min v controls;  $p < 0.01$ ). Symptom intensities after a nutrient challenge were significantly higher in FD patients and symptomatic blood donors compared with asymptomatic controls; 14 of 48 blood donors with symptoms and 16 of 40 patients had a symptom response to the nutrient challenge exceeding the response (mean (2SD)) of healthy asymptomatic controls. **Conclusion:** Gastric emptying and the global symptom response to a standardised nutrient challenge are abnormal in population based (non-health care seeking) subjects with dyspepsia.