

Functional Bowel Disorders



Recent Advances 16

A review of current literature by
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Editorial Policy

Despite accounting for a major portion of the gastroenterologist's workload, functional bowel disorders still receive relatively little attention from a research point of view - although there are signs that this situation may be slowly changing. The major journals are not overburdened with papers on the subject and consequently definitive publications tend to be scattered throughout the literature and hard to track down. Furthermore, for those of us undertaking research in this area, presenting work at major meetings can pose difficulties as many learned societies do not even have a functional bowel category. Authors are then left with the problem of having to decide, to which of a series of sections, such as "stomach", "colon", "colorectal" or "motility", their work is most suited. Fortunately, the American Gastroenterological Association has had the foresight to introduce a functional bowel disorder category and it is to be hoped that others will follow this lead.

The purpose of this booklet is to try and bring together under one cover as many publications as possible on the subject of functional bowel disorders relevant to clinical practice. The references are listed under five main headings: "irritable bowel syndrome", "functional dyspepsia", "functional oesophageal disorders", "pharmacology" and "miscellaneous" - inevitably, this latter heading contains an assortment of conditions that some

people might classify differently. However, these categories are only intended as a general guide and when a paper covers several topics, it may be listed in more than one place. In some cases it can be difficult to decide whether a topic should be classified under functional bowel disorders at all and some arbitrary decisions had to be made. For instance, we decided to exclude the majority of oesophageal disorders because they are covered adequately elsewhere. Thus, we have only listed references on oesophageal problems where a strong functional element is currently suggested - eg. angiogram negative chest pain. In order to facilitate more selective scanning of titles, each heading is further sub-divided into clinical and non-clinical with the latter covering items of a more mechanistic nature. Animal work has been excluded all together.

Each issue is accompanied by a brief editorial written around a collection of publications which either illustrate a particular theme or are especially topical. The abstracts of papers chosen for editorial comment are published in full but in no way does this imply that these are necessarily judged to be the best pieces of research for the period covered by that issue of booklet.

We hope this booklet will help to keep busy clinicians abreast of developments in the world of functional bowel disorders and possibly stimulate further research in this difficult area.

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Review of abstracts

The successful treatment of patients with functional gastrointestinal disorders continues to be challenging and the development and identification of new compounds which are safe and effective even more demanding. Part of these difficulties stem from incomplete understanding of the aetiology and pathophysiology of these disorders, which are likely to vary across the sub-classifications. This is further complicated by the recent findings that 75% of IBS patients change from one sub-group to another at least once per year, with mixed IBS been the least stable, most often changing to IBS with constipation (IBS-C) ¹. The least likely change appears to be from IBS with diarrhea (IBS-D) to IBS-C and vice versa ¹. As well as being less stable ^{1,2}, IBS with a mixed or alternating bowel habit tends to exhibit a greater prevalence of psychological and extraintestinal symptomatology than either IBS-C or -D ². Other confounding factors include the overlap of IBS with other disorders, such as gastro-oesophageal reflux disease ^{3,4} and even renal disorders ^{5,6,7}. It is interesting to note that symptoms of IBS or functional dyspepsia are especially common in women reporting domestic violence to the police ⁸ and those who have experienced sexual abuse, despite having worse symptomatology than non-sexually abused IBS patients, seem to be more likely to improve following psychological treatment ⁹. Furthermore, measuring rectal luminal concentrations of nitric oxide (NO) may be of use in discriminating patients with functional from organic gastrointestinal disease ¹⁰. In addition, the impairment of quality of life in IBS appears to be related more to extraintestinal symptomatology rather than the traditional gut related symptoms of the condition ¹¹ and the treatment received by IBS patients appears to be influenced by the physicians level of knowledge of gender issues in IBS, and even the gender of the physicians themselves ¹².

Meta-analyses of randomized controlled clinical trials in functional gastrointestinal disorders has shown that the placebo response varies from 16 to over 70% ¹³ and appears to depend on the frequency of intervention ^{13,14}, the overall treatment effect of the active agent being studied ¹³ and whether the patients studied have been defined using specific criteria, such as the Rome criteria ¹⁴. Despite the high placebo response in such trials, this value is not dissimilar to that observed in non-intestinal diseases, such as depression, and even organic gastrointestinal diseases such as inflammatory bowel disease ¹⁵. Furthermore, placebo analgesic effects over time appear to be related to a reduction in negative emotions, such as expected pain levels, desire for pain relief and anxiety rather than to endogenous opioid mechanisms ¹⁶.

Since our last issue there has been a spate of publications on the effects of alternative medications for the treatment of functional gastrointestinal disorders, with a probiotic containing *Bifidobacterium infantis* being shown to be associated with a significant amelioration of symptoms ^{17,18} and normalization of the ratio of an anti-inflammatory to a pro-inflammatory cytokine (IL-10/IL-12) ¹⁸, whilst those containing *Lactobacillus* were no better than placebo at relieving symptoms in patients with IBS ¹⁸, although there may be an effect on perceived abdominal distension but not pain in children with IBS ¹⁹. Moreover, a symbiotic SCM-III has been shown to be 'effective' or 'very effective' in more than 80% of patients with IBS with less than 5% reporting it to be 'not effective' compared with 40% on placebo ²⁰. Abdominal pain and bloating along with bowel habit significantly improved with this preparation, especially in those with constipation or alternating bowel habit ²⁰. There is evidence that IBS patients may have altered gastrointestinal microbial flora compared with healthy controls ²¹ and this provides one rationale



for the use of pro-biotics in this condition although these organisms have a wide range of other potentially useful activities. Other studies using non-pharmacological approaches include one assessing beidellitic montmorillonite, a purified clay containing a double aluminium and magnesium silicate which appears to help pain but not bowel habit in patients with constipation predominant IBS²², and a number assessing various herbal preparations^{23,24,25,26}. A meta-analysis on the effect of STW 5 (Iberogast) suggests a positive effect on dyspeptic symptoms²⁴ and this compound also appears to improve antral contractility at least in an in-vitro preparation²⁶.

Attempts to unravel the pathophysiology of functional disorders continues with studies suggesting blunted pituitary and adrenocortical responsiveness in patients with IBS and functional dyspepsia²⁷, dysfunction of the CCK system in IBS²⁸, down regulation of contractile G proteins and up-regulation of inhibitory G proteins, possibly caused by overexpression of progesterone receptors in patients with slow transit chronic constipation²⁹ and increased intestinal permeability irrespective of a previous episode of gastroenteritis in patients with IBS³⁰. There appears to be a direct correlation between dyspeptic symptoms and circulating acylated ghrelin concentration in patients with functional dyspepsia³¹, and from the journal called *Medical Hypotheses* comes the suggestion that lateral medullary ischaemia at the microvascular level may lead to IBS³². However, alterations in visceral sensation and the mechanisms associated with these changes are still the focus of much research, with recent studies suggesting that IBS-C patients have increased beta-adrenergic activity which directly correlates with visceral sensation³³, that an exclusion diet based on the presence of elevated IgG4 food antibodies not only improves

symptoms but also increases rectal compliance without any concomitant change in sensitivity³⁴, that rectal hyposensitivity in patients with constipation is related to increased compliance in some but in others is associated with impairment of the afferent pathways³⁵ and that although acute stress alters gut-specific efferent autonomic innervation, as shown by a reduction in rectal mucosal blood flow in both IBS and non-IBS subjects, it only increases sensitivity in patients with IBS, suggesting the involvement of different regulatory mechanisms, either central or peripheral in such individuals³⁶. Patients with IBS often complain of bladder symptoms and it is therefore of interest to note that patients with interstitial cystitis appear to have rather similar responses to somatic stimuli to those observed in IBS, suggesting altered central mechanisms in processing sensory events from the bladder³⁷.

New insights into the response of the brain to visceral stimuli include a study suggesting that the tricyclic antidepressant amitriptyline reduces brain activation to painful rectal distension only in the presence of concomitant stress³⁸ and another suggesting that patients with quiescent ulcerative colitis, unlike those with IBS, do not necessarily exhibit increased visceral afferent input to the brain during rectal distension³⁹. IBS patients exhibited greater activation of the limbic/paralimbic circuits whilst these circuits appear to be inhibited in quiescent ulcerative colitis and healthy controls by the right lateral frontal cortex³⁹. Finally we end with some work on IBS in childhood^{40,41,42} and the continuing debate that there may be a genetic contribution to gastrointestinal dysfunction with one study suggesting a role of a CCK-1 gene polymorphism in delaying gastric emptying and another suggesting genetic factors have little influence in IBS^{43,44}.



1. A prospective assessment of bowel habit in irritable bowel syndrome in women: defining an alternator.

Drossman DA, Morris CB, Hu Y, Toner BB, Diamant N, Leserman J, Shetzline M, Dalton C, Bangdiwala SI
Gastroenterology, 2005, 128 (3), 580-9.

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is subtyped as IBS with diarrhea (IBS-D) or IBS with constipation (IBS-C) based on Rome II guidelines. The remaining group is considered as having mixed IBS (IBS-M). There is no standard definition of an alternator (IBS-A), in which bowel habit changes over time. Our aim was to use Rome II criteria to prospectively assess change in bowel habit for more than 1 year to understand IBS-A. **METHODS:** Female patients (n=317) with IBS entering a National Institutes of Health treatment trial were studied at baseline with questionnaires and 2-week daily diary cards of pain and stool frequency and consistency. Studies were repeated at the end of treatment (3 months) and at four 3-month intervals for one more year. Algorithms to classify subjects into IBS-D, IBS-C, and IBS-M groups used diary card information and modified Rome II definitions. Changes in bowel habit at 3-month intervals were then assessed using these surrogate diary card measures. **RESULTS:** At baseline, 36% had IBS-D, 31% IBS-M, and 34% IBS-C. Except for stool frequency, there were no differences between groups. While the proportion of subjects in each subgroup remained the same over the year, most individuals (more than 75%) changed to either of the other 2 subtypes at least once. IBS-M was the least stable (50% changed out by 12 weeks). Patients were more likely to transition between IBS-M and IBS-C than between IBS-D and IBS-M. Notably, only 29% switched between the IBS-D and IBS-C subtypes over the year. **CONCLUSIONS:** While the proportion of subjects in each of the IBS subtypes stays the same, individuals commonly transition between subtypes, particularly between IBS-M and IBS-C. We recommend that IBS-A be defined as at least one change between IBS-D and IBS-C by Rome II criteria over a 1-year period.

2. Characterization of the alternating bowel habit subtype in patients with irritable bowel syndrome.

Tillisch K, Labus JS, Naliboff BD, Bolus R, Shetzline M, Mayer EA, Chang L
The American journal of gastroenterology, 2005, 100 (4), 896-904.

BACKGROUND: Due to a wide range of symptom patterns, patients with irritable bowel syndrome (IBS) are often subgrouped by bowel habit. However, the IBS subgroup with alternating bowel habits (IBS-A) has been poorly characterized. **OBJECTIVES:** (i) To determine a set of bowel

habit symptom criteria, which most specifically identifies IBS patients with an alternating bowel habit, (ii) to describe IBS-A bowel symptom patterns, and (iii) to compare clinical characteristics among IBS-A, constipation-predominant (IBS-C), and diarrhea-predominant IBS (IBS-D). **METHODS:** One thousand one hundred and two Rome I positive IBS patients were analyzed. Three sets of potential criteria for IBS-A were developed and compared by multirater Kappa test. Gastrointestinal, psychological, extraintestinal symptoms, and health-related quality of life were compared in IBS-A, IBS-C, and IBS-D using chi(2) test and analysis of variance (ANOVA). **RESULTS:** Stool consistency was determined to be the most specific criteria for alternating bowel habits. IBS-A patients reported rapid fluctuations in bowel habits with short symptom flares and remissions. There was a greater prevalence of psychological and extraintestinal symptoms in the IBS-A subgroup compared to IBS-C and IBS-D. No differences were seen between bowel habit subtypes in health-related quality of life. **CONCLUSIONS:** IBS-A patients have rapidly fluctuating symptoms and increased psychological comorbidity, which should be taken into account for clinical practice and clinical trials.

3. Prevalence of functional gastrointestinal disorders in a population of subjects consulting for gastroesophageal reflux disease in general practice.

Guillemot F, Ducrotte P, Bueno L
Gastroenterologie clinique et biologique, 2005, 29 (3), 243-6.

AIMS: To establish the prevalence of functional gastrointestinal (GI) disorders in adult patients with symptoms of gastroesophageal reflux disease (GERD) and to assess the impact of GERD treatment on functional GI disorders in medical practice in France. **METHODS:** 3318 patients with GERD symptoms (mean age 53 yr; 1726 women and 1592 men) were involved in the survey. A questionnaire on demographic data, GERD features, presence of functional GI disorders and their features, and impact of GERD treatment on functional GI disorders was performed by the physician. The size of the different groups was compared using either a chi2 test or a Mantel-Haenszel analysis, on a case by case basis. **RESULTS:** Seventy-two percent of patients with GERD had associated functional GI disorders, with a mean of 4.1 +/- 1.9 functional digestive symptoms per patient. Gas, flatulence, transit disorders and abdominal distension were the most commonly reported symptoms. Among patients with functional GI symptoms, 27% had symptoms suggestive of irritable bowel syndrome (IBS), 16% were suggestive of dyspepsia while 57% had



both upper and lower functional digestive symptoms. According to the patients, GERD treatment had a positive impact (significant to complete improvement) on their functional GI disorders in about one-third of patients particularly in those with dyspeptic-type symptoms. CONCLUSIONS: Functional GI disorders are particularly common in adult patients suffering from GERD, with a three times higher prevalence than in the general population.

4. Irritable bowel, smoking and oesophageal acid exposure: an insight into the nature of symptoms of gastro-oesophageal reflux.

Zimmerman J

Alimentary pharmacology & therapeutics, 2004, 20 (11-12), 1297-303.

BACKGROUND: In gastro-oesophageal reflux disease, oesophageal acid exposure correlates with symptoms but explains only a small fraction of their variance. AIMS: To elucidate the effects of irritable bowel syndrome and smoking on gastro-oesophageal reflux disease symptoms and to clarify whether they modulate the relationship between oesophageal acid exposure and symptoms. METHODS: The relationship between oesophageal acid exposure, irritable bowel syndrome (Rome I criteria), smoking status and symptoms was investigated in patients with a normal gastroscopy who underwent a 24-h oesophageal pH monitoring. RESULTS: Of 256 patients with gastro-oesophageal reflux disease, 16% were smokers and 50% met the criteria for irritable bowel syndrome (irritable bowel syndrome+). The extent of oesophageal acid exposure was unrelated to smoking or irritable bowel syndrome status. Oesophageal acid exposure, irritable bowel syndrome status and current smoking independently predicted symptoms. Irritable bowel syndrome and smoking modulated the effect of oesophageal acid exposure on symptoms: oesophageal acid exposure was predictive of symptoms only in non-smokers. However, irritable bowel syndrome was a significant predictor of symptoms both in smokers and in non-smokers. Smoking was associated with symptoms only in irritable bowel syndrome+, while oesophageal acid exposure was associated with symptoms irrespective of irritable bowel syndrome status. CONCLUSIONS: In patients with non-erosive gastro-oesophageal reflux disease, smoking and irritable bowel syndrome independently predicted symptoms, without affecting the extent of oesophageal acid exposure. The relationship between oesophageal acid exposure and symptoms was affected significantly, and in opposite directions, by smoking and irritable bowel syndrome.

5. High prevalence of irritable bowel syndrome and upper gastrointestinal symptoms in patients with chronic renal failure.

Kahvecioglu S, Akdag I, Kiyici M, Gullulu M, Yavuz M, Ersoy A, Dilek K, Yurtkuran M
Journal of nephrology, 2005, 18 (1), 61-6.

BACKGROUND: Gastrointestinal symptoms and psychiatric disorders are common among patients with chronic renal failure since uremia affects all systems as well as the gastrointestinal tract. Irritable bowel syndrome (IBS) is a frequent functional disorder worldwide. We aimed to evaluate the frequency of IBS and upper gastrointestinal symptoms in patients with chronic renal failure (CRF). The relationships between IBS, sex and additional psychiatric disorders in the same patient group were determined and results were compared with controls. METHODS: Ninety-three hemodialysis (HD) and 35 peritoneal dialysis (PD) patients and 51 healthy volunteers were enrolled in this cross-sectional study. They completed the questionnaires that were later evaluated to determine the frequency of IBS in HD, PD and control groups; the frequency of depression and anxiety in these three groups and their relationship to sex. Symptoms of upper gastrointestinal system and their relation to sex were also investigated in all groups. RESULTS: In this study, we have demonstrated that prevalence of IBS in patients with chronic renal failure on hemodialysis or peritoneal dialysis is higher than the controls though the type of dialysis does not seem to influence the IBS prevalence itself. Epigastric pain was more prevalent in HD patients than PD patients. CONCLUSIONS: The present study suggests that though IBS is common in patients with CRF, it is generally underestimated. Type of dialysis does not seem to change the clinical picture much. Accompanying mood disorders must also be taken into consideration.

6. Renal tubular proteinuria in patients with irritable bowel syndrome.

O'Brien AJ, Lamb EJ, Muller AF

European journal of gastroenterology & hepatology, 2005, 17 (1), 69-72.

OBJECTIVE: Irritable bowel syndrome (IBS) is a common condition that is poorly understood. We have previously demonstrated tubular proteinuria in patients with inflammatory bowel disease. This study examined whether tubular proteinuria was a feature of IBS. METHODS: Eighty control subjects (male:female, 28:52; age range 20-65 years) and 21 patients with IBS (male:female, 9:12; age range 16-64 years) (not significant) were recruited. Patients with known renal disease, hypertension, diabetes or



microbiological evidence of urinary infection were excluded. The IBS patients all fulfilled the ROME II criteria. None had preceding gastroenteritis. Urinary alpha1-microglobulin (alpha1-M) was measured in a second-voided morning urine sample and corrected for urinary concentration by measurement of creatinine. Blood samples were analysed for haematochemical indices including C-reactive protein. Statistical analysis was by unpaired t test. RESULTS: None of the IBS patients were reclassified with inflammatory bowel disease over a 5-year follow up period. All had normal haematochemical parameters. Mean +/- standard deviation urinary alpha1-M concentrations were significantly higher in IBS patients than controls (IBS patients, 1.17 +/- 0.65 mg/mmol; controls, 0.75 +/- 0.36 mg/mmol; $P < 0.01$) and exceeded 1.5 mg/mmol (the upper reference limit) in seven patients. There was no difference in urinary alpha1-M concentrations in the diarrhoea-predominant and constipation-predominant groups (mean +/- standard deviation, 1.342 +/- 0.65 versus 0.76 +/- 0.48 mg/mmol; $P = 0.062$). CONCLUSIONS: Urinary alpha1-M concentration is commonly increased in IBS, suggesting the presence of renal proximal tubular injury.

7. Risk of irritable bowel syndrome and depression in women with interstitial cystitis: a case-control study.

Novi JM, Jeronis S, Srinivas S, Srinivasan R, Morgan MA, Arya LA

The Journal of urology, 2005, 174 (3), 937-40.

PURPOSE: We determined the risk of irritable bowel syndrome and depression in women with interstitial cystitis. **MATERIALS AND METHODS:** Cases consisted of 46 women with newly diagnosed interstitial cystitis. The control group consisted of 46 women presenting for an annual gynecologic examination. Data were collected using standardized, validated questionnaires. **RESULTS:** The 2 groups were similar with respect to age, race, parity, previous pelvic surgery and postmenopausal hormone use. Compared with controls patients with interstitial cystitis were more likely to be diagnosed with irritable bowel syndrome (OR 11, 95% CI 2.7 to 52, $p < 0.001$) and depression (OR 3.97, 95% CI 1.17 to 14.1, $p < 0.05$). In the interstitial cystitis group when we compared women with and without depression, we noted that women with depression were significantly more likely to complain of bladder pain, nocturia, abdominal pain and other bowel symptoms. **CONCLUSIONS:** The association of irritable bowel syndrome and depression appears to be greater in women with interstitial cystitis than in controls. Additionally, it appears that pain of bladder or bowel origin is a significant cause of depression in women with interstitial cystitis.

8. Prevalence of functional gastrointestinal disorders in women who report domestic violence to the police.

Perona M, Benasayag R, Perello A, Santos J, Zarate N, Zarate P, Mearin F

Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 2005, 3 (5), 436-41.

BACKGROUND & AIMS: Retrospective studies found an association between past sexual, physical, or psychological abuse and functional gastrointestinal disorders (FGIDs). However, there are no studies evaluating such an association concurrently with the ongoing abuse. Our aim was to investigate the prevalence of the main FGIDs, functional dyspepsia and irritable bowel syndrome, in 70 women reporting a situation of domestic violence to the police and to evaluate the level of psychological distress and its relationship with the presence of FGID. **METHODS:** Through an interview between a social worker and the woman reporting abuse, digestive symptoms, psychological status, and type of abuse were recorded. These data were matched against police records. Functional dyspepsia and irritable bowel syndrome were diagnosed according to Rome II criteria. **RESULTS:** Seventy-one percent of the women had an FGID: 67% functional dyspepsia, 47% irritable bowel syndrome, and 43% both. In two thirds of the cases, FGID onset occurred simultaneously with or soon after abuse onset. Only 34% of the women had sought medical attention for FGID symptoms. No differences were found between women with or without FGID regarding age and type or duration of abuse; psychological distress tended to be more severe in the group of women with FGIDs. **CONCLUSIONS:** Most women who suffer domestic violence (reported to the police) have functional dyspepsia and/or irritable bowel syndrome and also have elevated psychological distress. This has important implications, not only for comprehensive health care of women in a situation of abuse, but also for medical treatment of women with FGIDs.

9. Reported sexual abuse predicts impaired functioning but a good response to psychological treatments in patients with severe irritable bowel syndrome.

Creed F, Guthrie E, Ratcliffe J, Fernandes L, Rigby C, Tomenson B, Read N, Thompson DG

Psychosomatic Medicine, 2005, 67 (3), 490-499.

OBJECTIVE: We assessed the effect of reported sexual abuse on symptom severity and health-related quality of life in patients with severe irritable bowel syndrome (IBS) undergoing psychological treatments. **Methods:** IBS patients entering a treatment trial who reported prior sexual abuse



were compared with the remainder in terms of symptom severity and health-related quality of life (SF-36) at trial entry and 15 months later. Analyses used ANCOVA with age, sex, marital status, and treatment group as covariates. We assessed possible mediators using multiple regression analysis. Results: Of 257 patients with severe IBS, 31 (12.1%) reported a history of rape and 28 (10.9%) reported forced, unwanted touching. People who reported abuse were more impaired than the remainder on the SF-36 scales for pain (adjusted $p = .023$) and physical function ($p = .029$); these relationships followed a "dose-response" relationship and were mediated by SCL-90 somatization score. At 15 months follow-up, the associations between reported abuse and SF-36 scores were lost because people with reported abuse, especially rape, improved more than the remainder when treated with psychotherapy or paroxetine (selective serotonin reuptake inhibitor antidepressant); this improvement was mediated by change in SCL-90 somatization score. Conclusions: In severe IBS, the association between self-reported sexual abuse and impaired functioning is mediated by a general tendency to report numerous bodily symptoms. A reported history of abuse is associated with a marked improvement following psychological treatment. Copyright (C) 2005 by the American Psychosomatic Society.

10. Rectal mucosal nitric oxide in differentiation of inflammatory bowel disease and irritable bowel syndrome.

Reinders CI, Herulf M, Ljung T, Hollenberg J, Weitzberg E, Lundberg JO, Hellstroem PM
Clinical Gastroenterology and Hepatology, 2005, 3 (8), 777-783.

Background & Aims: Differentiating patients with functional bowel disorders from those with inflammatory bowel disease (IBD) can be difficult. Rectal luminal levels of nitric oxide (NO) are greatly increased in IBD. To further evaluate this disease marker, we compared NO in patients with irritable bowel syndrome (IBS) with those found in patients with active IBD and in healthy control subjects. Methods: Rectal NO was measured with chemiluminescence technique by using a tonometric balloon method in 28 healthy volunteers, 39 patients with IBS, 86 with IBD (Crohn's disease and ulcerative colitis), and 12 patients with collagenous colitis. In addition, NO was measured before and after a 4-week treatment period in patients with active ulcerative colitis and repeatedly during 2 weeks in healthy volunteers. Results: NO was low in healthy control subjects (median, 45; 25th-75th percentile, 34-64 parts per billion [ppb]), and variations over time were small. In IBS patients

NO was slightly increased (150, 53-200 ppb; $P < .001$), whereas patients with active IBD or collagenous colitis had greatly increased NO levels (3475, 575-8850 ppb, and 9950, 4475-19,750 ppb, respectively; $P < .001$). With a cutoff level of 250 ppb, NO had a sensitivity of 95% and a specificity of 91% in discriminating between active bowel inflammation and IBS. Rectal NO correlated with disease activity in IBD and collagenous colitis and decreased markedly in IBD patients responding to anti-inflammatory treatment. Conclusions: Rectal NO is a minimally invasive and rapid tool for discriminating between active bowel inflammation and IBS and a possibly useful add-on for monitoring patients with IBD. (C) 2005 by the American Gastroenterological Association.

11. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome.

Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, Naliboff B
Archives of internal medicine, 2004, 164 (16), 1773-80.

BACKGROUND: Current guidelines recommend routine assessment of health-related quality of life (HRQOL) in patients with irritable bowel syndrome (IBS). However, physicians rarely have the time to measure HRQOL with the appropriate methodological rigor, and data suggest that HRQOL in patients with IBS is often estimated using inaccurate clinical gestalt. The identification of predictive factors could allow physicians to better assess HRQOL without using misleading clinical clues. We, therefore, sought to identify determinants of HRQOL in patients with IBS. METHODS: We examined 770 patients, 18 years or older, with IBS at a university-based referral center. Subjects completed a symptom questionnaire, the Symptoms Checklist-90 items psychometric checklist, and the 36-Item Short-Form Health Survey. The main outcome was HRQOL as measured by the mental and physical component scores of the 36-Item Short-Form Health Survey. We first developed a list of hypothesis-driven HRQOL predictors, and then performed multivariate regression analysis to measure the independent association of each predictor with HRQOL. RESULTS: Seven factors ($r(2) = 0.39$) independently predicted physical HRQOL: (1) more than 5 physician visits per year, (2) tiring easily, (3) low in energy, (4) severe symptoms, (5) predominantly painful symptoms, (6) the feeling that there is "something seriously wrong with body," and (7) symptom flares for longer than 24 hours. Eight factors ($r(2) = 0.36$) independently predicted mental HRQOL: (1) feeling tense, (2) feeling nervous, (3) feeling hopeless, (4) difficulty sleeping, (5) tiring easily, (6) low sexual interest, (7) IBS symptom interference with sexual function, and (8)



low energy. CONCLUSIONS: Health-related quality of life in patients with IBS is primarily related to extraintestinal symptoms rather than traditionally elicited gastrointestinal symptoms. These findings suggest that rather than focusing on physiological epiphenomena (stool characteristics and subtype of IBS) and potentially misleading clinical factors (age and disease duration), physicians might be better served to gauge global symptom severity, address anxiety, and eliminate factors contributing to chronic stress in patients with IBS.

12. Male and female physicians show different patterns of gender bias: A paper-case study of management of irritable bowel syndrome.

Hamberg K, Risberg G, Johansson EE
Scandinavian Journal of Public Health, 2004, 32 (2), 144-152.

Aims: Research has raised concerns about gender bias in medicine, i.e. that men and women might be treated differently due to gender-stereotyped attitudes among physicians. The authors investigated gender differences in medical management of a common health problem, irritable bowel syndrome (IBS). Method: In a national examination for Swedish house officers, the examinees were allocated to suggest management of IBS in either a male or female paper-patient. The case description was identical in both genders with the exception of prior prostate and gynaecological symptoms. The open answers were coded for analysis. A total of 289 physicians (45% women) participated. Chi-squared tests were used to measure differences in proportions. Results: In variables focusing on medication, weight, gynaecological problems, tobacco, alcohol, thyroid function, proposed diagnoses, X-ray of the colon, and advice about lifestyle, significant or close to significant gender differences were seen. Both male and female physicians made gender differences but they did not show the same pattern of differences. Conclusions: The results suggest that gender bias is involved in medical management of IBS but men and women physicians may show disparate patterns of gender bias. There is a need for larger studies on gender differences in medical management with designs making it possible to consider the gender of both the patient and the physician. Furthermore, the results call attention to 'knowledge-mediated gender bias', a phenomenon implying that once knowledge about gender differences in a condition has been established, this might in fact cause gender-biased assessments of individual patients in clinical practice. (C) Taylor & Francis 2004.

13. Defining the predictors of the placebo response in irritable bowel syndrome.

Pitz M, Cheang M, Bernstein CN
Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 2005, 3 (3), 237-47.

BACKGROUND AND AIMS: We sought to determine the components of irritable bowel syndrome (IBS) clinical trials that correlate with higher levels of placebo response. METHODS: We performed a systematic review of placebo-controlled trials in patients with IBS to assess which variables correlate with a higher placebo response. Placebo responses for global symptom improvement and for decreased abdominal pain were assessed. Univariate and multiple linear regression analyses were conducted. RESULTS: Higher rates of global improvement correlated with frequency of administration of study intervention ($r = .31$, $P = .03$), duration of the study ($r = .28$, $P = .04$), and overall treatment effect of the active agent being studied ($r = .33$, $P = .02$). Higher rates of decreased abdominal pain correlated with the frequency of intervention ($r = .39$, $P = .02$) and overall treatment effect ($r = .40$, $P = .01$), whereas lower placebo response rates correlated with year of the study ($r = -.36$, $P = .03$), median age ($r = -.38$, $P = .04$), and duration of study run-in period ($r = -.33$, $P = .04$). On multivariate analysis, global improvement in the placebo group was associated significantly with intervention frequency ($P = .0079$), overall treatment response ($P = .0031$), and parallel study design ($P = .0044$). Decreased abdominal pain was associated significantly with frequency of intervention ($P = .0061$) and overall treatment response ($P = .0128$). CONCLUSIONS: In IBS studies, higher placebo response rates correlated with frequency of the intervention and with overall treatment effect of the active agent being studied. In designing IBS trials, it may be possible to minimize placebo response by less frequent dosing. In treating patients with IBS, it may be possible to harness the placebo response and maximize therapeutic response rates by more frequent dosing.

14. The placebo effect in irritable bowel syndrome trials: a meta-analysis.

Patel SM, Stason WB, Legedza A, Ock SM, Kaptchuk TJ, Conboy L, Canenguez K, Park JK, Kelly E, Jacobson E, Kerr CE, Lembo AJ
Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society, 2005, 17 (3), 332-40.

BACKGROUND: Despite the apparent high placebo response rate in randomized placebo-controlled trials (RCT) of



patients with irritable bowel syndrome (IBS), little is known about the variability and predictors of this response. **OBJECTIVES:** To describe the magnitude of response in placebo arms of IBS clinical trials and to identify which factors predict the variability of the placebo response. **METHODS:** We performed a meta-analysis of published, English language, RCT with 20 or more IBS patients who were treated for at least 2 weeks. This analysis is limited to studies that assessed global response (improvement in overall symptoms). The variables considered as potential placebo modifiers were study design, study duration, use of a run-in phase, Jadad score, entry criteria, number of office visits, number of office visits/study duration, use of diagnostic testing, gender, age and type of medication studied. **FINDINGS:** Forty-five placebo-controlled RCTs met the inclusion criteria. The placebo response ranged from 16.0 to 71.4% with a population-weighted average of 40.2%, 95% CI (35.9–44.4). Significant associations with lower placebo response rates were fulfillment of the Rome criteria for study entry ($P=0.049$) and an increased number of office visits ($P=0.026$). **CONCLUSIONS:** Placebo effects in IBS clinical trials measuring a global outcome are highly variable. Entry criteria and number of office visits are significant predictors of the placebo response. More stringent entry criteria and an increased number of office visits appear to independently decrease the placebo response.

15. The placebo response in functional bowel disorders: perspectives and putative mechanisms.

Enck P, Klosterhalfen S

Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society, 2005, 17 (3), 325-31.

The nature and determinants of the placebo response are widely unknown, as are the underlying psychological and biological mechanisms. High placebo response rates in functional bowel disorders (functional dyspepsia, irritable bowel syndrome) are similar to those in non-intestinal diseases (depression, pain, Parkinson's disease) and not too dissimilar to other organic gastrointestinal diseases (duodenal ulcer, inflammatory bowel diseases).

Methodological reasons (regression to the mean, shift in signal detection through manipulation of expectations) and psycho-biological mechanisms (Pavlovian conditioning of biological processes) are proposed to explain a large component of the response variance in clinical trials. Psychobiological mechanisms of the placebo response in functional and organic diseases can also be identified in brain function studies (such as imaging).

16. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms.

Vase L, Robinson ME, Verne GN, Price DD
Pain, 2005, 115 (3), 338-47.

A study was conducted to determine whether changes in expected pain levels, desire for pain relief, or anxiety contribute to an increase in placebo analgesia over time as well as to determine whether placebo analgesic effects of IBS patients are related to endogenous opioid mechanisms. Twenty-six women with IBS were exposed to rectal stimulation (35 or 55 mmHg for 30 s) and tested under natural history (NH), rectal placebo (RP) and rectal lidocaine (RL) conditions. During all conditions, 16 patients were given saline intravenously (to test for a placebo effect) and 10 patients were given naloxone intravenously (to test naloxone antagonism of the placebo effect) on a double blind basis. Patients rated expected pain level, desire for pain relief and anxiety at 2 and 22 min after the onset of NH, RP, and RL conditions and they rated actual pain intensity at 5-min intervals for 40 min. There was a large and significant placebo effect ($P<0.001$) that increased over time. Ratings of expected pain levels, desire for pain relief and anxiety decreased over time and contributed to more variance in placebo and lidocaine responses during the last half of the session. These changes suggest that a reduction in negative emotions may be central to placebo effects. There was no significant difference between psychological mediators (desire, expectation, anxiety) or the placebo effect in the saline and naloxone groups, indicating that neither the psychological mediators nor the placebo analgesic effect were associated with endogenous opioids in this clinically related paradigm.

17. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: A controlled 6-month intervention.

Kajander K, Hatakka K, Poussa T, Faerkkilae M, Korpela R
Alimentary Pharmacology and Therapeutics, 2005, 22 (5), 387-394.

Background: Irritable bowel syndrome is a gastrointestinal disorder of unknown aetiology. The effect of probiotics in this syndrome remains unclear. Aim: To investigate whether a probiotic mixture containing *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99 and *Propionibacterium freudenreichii* ssp. *shermanii* JS is effective in alleviating irritable bowel syndrome symptoms. Methods: A total of 103 patients fulfilling the Rome I or II criteria took part in this 6-month, randomized, double-blind



placebo-controlled trial. The patients received a probiotic capsule or a placebo capsule daily. Gastrointestinal symptoms and bowel habits were recorded. Results: At the end the total symptom score (abdominal pain + distension + flatulence + borborygmi) was 7.7 (95% CI: -13.9 to -1.6) points lower in the probiotic group ($P = 0.015$). This represents a median reduction of 42% in the symptom score of the probiotic group compared with 6% in the placebo group. In individual symptoms, borborygmi was milder in the probiotic group ($P = 0.008$), and for the rest of the symptoms there was a non-significant trend. Conclusions: The results indicate that this probiotic mixture is effective in alleviating irritable bowel syndrome symptoms. Considering the high prevalence of irritable bowel syndrome and the lack of effective therapies, even a slight reduction in symptoms could have positive public health consequences. (C) 2005 Blackwell Publishing Ltd.

18. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles.

O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM *Gastroenterology*, 2005, 128 (3), 541-51.

BACKGROUND & AIMS: The aim of this study was to compare the response of symptoms and cytokine ratios in irritable bowel syndrome (IBS) with ingestion of probiotic preparations containing a lactobacillus or bifidobacterium strain. **METHODS:** Seventy-seven subjects with IBS were randomized to receive either *Lactobacillus salivarius* UCC4331 or *Bifidobacterium infantis* 35624, each in a dose of 1×10^{10} live bacterial cells in a malted milk drink, or the malted milk drink alone as placebo for 8 weeks. The cardinal symptoms of IBS were recorded on a daily basis and assessed each week. Quality of life assessment, stool microbiologic studies, and blood sampling for estimation of peripheral blood mononuclear cell release of the cytokines interleukin (IL)-10 and IL-12 were performed at the beginning and at the end of the treatment phase. **RESULTS:** For all symptoms, with the exception of bowel movement frequency and consistency, those randomized to *B infantis* 35624 experienced a greater reduction in symptom scores; composite and individual scores for abdominal pain/discomfort, bloating/distention, and bowel movement difficulty were significantly lower than for placebo for those randomized to *B infantis* 35624 for most weeks of the treatment phase. At baseline, patients with IBS demonstrated an abnormal IL-10/IL-12 ratio, indicative of a proinflammatory, Th-1 state. This ratio was normalized by *B infantis* 35624 feeding alone. **CONCLUSIONS:** *B infantis*

35624 alleviates symptoms in IBS; this symptomatic response was associated with normalization of the ratio of an anti-inflammatory to a proinflammatory cytokine, suggesting an immune-modulating role for this organism, in this disorder.

19. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial.

Bausserman M, Michail S
The Journal of pediatrics, 2005, 147 (2), 197-201.

OBJECTIVE: To determine whether oral administration of the probiotic *Lactobacillus GG* under randomized, double-blinded, placebo-controlled conditions would improve symptoms of irritable bowel syndrome (IBS) in children. **STUDY DESIGN:** Fifty children fulfilling the Rome II criteria for IBS were given *Lactobacillus GG* or placebo for 6 weeks. Response to therapy was recorded and collected on a weekly basis using the Gastrointestinal Symptom Rating Scale (GSRS). **RESULTS:** *Lactobacillus GG* was not superior to placebo in relieving abdominal pain (40.0% response rate in the placebo group vs 44.0% in the *Lactobacillus GG* group; $P=.774$). There was no difference in the other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention ($P=.02$ favoring *Lactobacillus GG*). **CONCLUSIONS:** *Lactobacillus GG* was not superior to placebo in the treatment of abdominal pain in children with IBS but may help relieve such symptoms as perceived abdominal distention.

20. Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome.

Tsuchiya J, Barreto R, Okura R, Kawakita S, Fesce E, Marotta F
Chinese journal of digestive diseases, 2004, 5 (4), 169-74.

OBJECTIVE: Experimental and clinical studies have shown that a novel symbiotic (known as SCM-III) exerts a beneficial effect on gut translocation and local and systemic inflammatory and microbial metabolic parameters. The present investigation was a preliminary trial on the effectiveness of SCM-III for irritable bowel syndrome (IBS). **METHODS:** Sixty-eight consecutive adult patients with IBS who were free from lactose malabsorption, abdominal surgery, overt psychiatric disorders and ongoing psychotropic drug therapy or ethanol abuse were studied prospectively and divided into 2 groups that were comparable for age, gender, body size, education and pattern of presenting symptoms. The 2 groups were blindly given for 12 weeks either SCM-III 10 mL t.i.d or the same



dosage of heat-inactivated symbiotic. RESULTS: Treatment with SCM-III was 'effective' or 'very effective' in more than 80% of the patients ($P < 0.01$ vs baseline values and control). Less than 5% reported 'not effective' as the final evaluation compared with over 40% of patients in the control group. After 6 weeks of treatment, a significant improvement of pain and bloating was reported in the treatment group compared with control and baseline values. There was also a benefit for bowel habits, mostly for patients with constipation or alternating bowel habits. No overt clinical or biochemical adverse side-effects were recorded. CONCLUSION: Compared with baseline values and the control group, SCM-III resulted in a significant increase in lactobacilla, eubacteria and bifidobacteria, which suggests that some selected IBS patients could benefit substantially from symbiotics, but the treatment may need to be given on a cyclic schedule because of the temporary modification of the fecal flora.

21. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR.

Malinen E, Rinttilä T, Kajander K, Maetoe J, Kassinen A, Krogius L, Saarela M, Korpela R, Palva A
The American journal of gastroenterology, 2005, 100 (2), 373-82.

OBJECTIVE: The gut microbiota may contribute to the onset and maintenance of irritable bowel syndrome (IBS). In this study, the microbiotas of patients suffering from IBS were compared with a control group devoid of gastrointestinal (GI) symptoms. METHODS: Fecal microbiota of patients ($n = 27$) fulfilling the Rome II criteria for IBS was compared with age- and gender-matched control subjects ($n = 22$). Fecal samples were obtained at 3 months intervals. Total bacterial DNA was analyzed by 20 quantitative real-time PCR assays covering approximately 300 bacterial species. RESULTS: Extensive individual variation was observed in the GI microbiota among both the IBS- and control groups. Sorting of the IBS patients according to the symptom subtypes (diarrhea, constipation, and alternating predominant type) revealed that lower amounts of *Lactobacillus* spp. were present in the samples of diarrhea predominant IBS patients whereas constipation predominant IBS patients carried increased amounts of *Veillonella* spp. Average results from three fecal samples suggested differences in the *Clostridium coccoides* subgroup and *Bifidobacterium catenulatum* group between IBS patients ($n = 21$) and controls ($n = 15$). Of the intestinal pathogens earlier associated with IBS, no indications of *Helicobacter* spp. or *Clostridium difficile* were found whereas one case of *Campylobacter jejuni* was identified by

sequencing. CONCLUSIONS: With these real-time PCR assays, quantitative alterations in the GI microbiota of IBS patients were found. Increasing microbial DNA sequence information will further allow designing of new real-time PCR assays for a more extensive analysis of intestinal microbes in IBS.

22. Symptomatic efficacy of beidellitic montmorillonite in irritable bowel syndrome: a randomized, controlled trial.

Ducrotte P, Dapoigny M, Bonaz B, Siproudhis L
Alimentary pharmacology & therapeutics, 2005, 21 (4), 435-44.

BACKGROUND: Beidellitic montmorillonite is a purified clay containing a double aluminium and magnesium silicate. AIM: To assess the efficacy and the safety of beidellitic montmorillonite (3 g, t.d. for 8 weeks) in patients with irritable bowel syndrome (IBS). METHODS: A multicentre, double-blind, placebo-controlled, randomized study with parallel groups, was performed in IBS patients selected according to ROME I criteria. Patients were included after a 1-week washout period to confirm that abdominal pain and/or discomfort was rated at least 2 on a 0-4 graded Likert scale. Patients were then randomized and stratified according to their predominant bowel habit profile into three groups. The use of rescue medication was allowed: polyethylene glycol 4000 (10-20 g/day) as a laxative agent in case of stool absence for three consecutive days, phloroglucinol (80 to a maximum of 320 mg/day) as a spasmolytic agent for no more than 8 days. The main end-point was the improvement of abdominal pain and/or discomfort by at least 1 point on the Likert scale. RESULTS: A total of 524 patients constituted the overall intent-to-treat population (ITT), 263 were assessed in the beidellitic montmorillonite group, i.e. 93 diarrhoea-predominant IBS (D-IBS), 83 constipation-predominant IBS (C-IBS), 87 alternating constipation/diarrhoea-IBS (A-IBS); 261 in the placebo group, i.e. 81 D-IBS, 92 C-IBS and 88 A-IBS. Initial analysis in the ITT population demonstrated a higher rate of success with beidellitic montmorillonite (51.7%) when compared with the placebo group (45.2%); however, the difference was not statistically significant. Improvement was significant in C-IBS both in ITT (beidellitic montmorillonite group = 49.4%, placebo group = 31.5%, $P < 0.016$) and per protocol populations (59.4% vs. 37.8%) ($P < 0.01$). The time to improvement of abdominal pain and/or discomfort (log Rank test) was also significantly in favour of beidellitic montmorillonite, ($P < 0.04$). The average number of stools per day was not different from baseline, either in all patients or in C-IBS patients. Spasmolytic and laxative agent intakes were not different between the two



groups. Subjective evaluation by patients of treatment efficacy and visual analogue scale test of treatment efficacy by investigators were significantly better in the beidellitic montmorillonite group ($P < 0.05$). Tolerance of beidellitic montmorillonite was considered optimal without any significant adverse event. CONCLUSIONS: Although pain or discomfort was not significantly improved in the entire IBS population treated with beidellitic montmorillonite in comparison with placebo, this study demonstrates that beidellitic montmorillonite is efficient for C-IBS patients ($P < 0.016$). This effect of beidellitic montmorillonite on pain cannot be explained by changes in bowel habits. The efficacy of this well-tolerated therapy warrants further confirmatory therapeutic trials in C-IBS patients.

23. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: A randomized, placebo-controlled, double-blind clinical trial.

Brinkhaus B, Hentschel C, Von Keudell C, Schindler G, Lindner M, Stuetzer H, Kohnen R, Willich SN, Lehmacher W, Hahn EG
Scandinavian Journal of Gastroenterology, 2005, 40 (8), 936-943.

OBJECTIVE: Irritable bowel syndrome (IBS) is a common functional disorder for which there is no reliable medical treatment. The aim of this study was to determine the efficacy of two herbal remedies used in the treatment of IBS. Material and methods. In a randomized, double-blind, placebo-controlled trial, IBS patients were randomly assigned to one of three treatment groups: 1) Curcuma xanthorrhiza 60 mg daily (curcuma group) ($n = 24$), 2) Fumaria officinalis 1500 mg daily (fumitory group) ($n = 24$) and 3) placebo ($n = 58$). The study treatment was applied three times a day for 18 weeks. The main outcome parameters were changes in global patient ratings of IBS-related pain and distension on a visual analogue scale (0-50 mm) between baseline and at the end of treatment. Additional outcome parameters included global assessments of changes in IBS symptoms and psychosocial stress caused by IBS. Results. A total of 106 patients (mean age 48 \pm 12 years, 63% F) were included in the intention-to-treat group. IBS-related pain decreased by -0.9 ± 11.5 (mm \pm SD) in the fumitory group, -0.3 ± 9.9 in the placebo group and increased by 2.0 ± 9.5 in the curcuma group ($p = 0.81$). IBS-related distension decreased by -1.4 ± 12.5 in the curcuma group, -2.1 ± 9.2 in the placebo group and increased by 0.3 ± 9.3 in the fumitory group ($p = 0.48$). Additionally, the global assessment of changes in IBS symptoms and psychological stress due to IBS did not differ significantly among the three treatment groups. Conclusions. Neither fumitory nor curcuma showed any

therapeutic benefit over placebo in patients with IBS. Therefore, the use of these herbs for the treatment of IBS cannot be recommended. (C) 2005 Taylor & Francis.

24. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast).

Melzer J, Roesch W, Reichling J, Brignoli R, Saller R
Alimentary pharmacology & therapeutics, 2004, 20 (11-12), 1279-87.

BACKGROUND: Despite a long-standing use of herbal drugs with dyspeptic symptoms, little attention has been paid to their clinical evaluation. AIM: To assess efficacy and safety of the herbal drug preparation STW 5 (containing, e.g. Iberis, peppermint, chamomile) in the treatment of functional dyspepsia. METHODS: Research in electronic databases, consultation of experts and of the producer identified STW 5 (Iberogast) as descriptor in six randomized-controlled trials. The raw data of three placebo-controlled studies which met the selection criteria, were reanalysed and pooled for meta-analysis; one reference-controlled study supported the safety analysis (STW 5: $n = 199$, control: $n = 198$). RESULTS: Pooled data showed verum ($n = 138$) to be more effective than placebo ($n = 135$) with regard to the severity of the most bothersome gastrointestinal symptom (P -value: 0.001, odds ratio: 0.22, 95% CI: 0.11-0.47). A fourth randomized-controlled trial showed no significant difference between STW 5 and cispapride. As to safety, adverse events were similar with verum and placebo; no serious adverse events occurred. DISCUSSIONS: From the point of view of efficacy and safety, the herbal medicinal product STW 5 appears to be a valid therapeutic option for patients seeking phytotherapy for their symptoms of functional dyspepsia.

25. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study.

Bundy R, Walker AF, Middleton RW, Booth J
The journal of alternative and complementary medicine: research on paradigm, practice, and policy, 2004, 10 (6), 1015-8.

OBJECTIVES: To assess the effects of turmeric (*Curcuma longa*) extract on irritable bowel syndrome (IBS) symptomology in otherwise healthy adults. DESIGN: Partially blinded, randomized, two-dose, pilot study. SUBJECTS: Five hundred (500) volunteers were screened for IBS using the Rome II criteria. Two hundred and seven (207) suitable volunteers were randomized. INTERVENTIONS: One or two tablets of a standardized turmeric extract taken daily for 8 weeks. OUTCOMES MEASURES: IBS prevalence,



symptom-related quality of life (IBSQOL) and self-reported effectiveness. RESULTS: IBS prevalence decreased significantly in both groups between screening and baseline (41% and 57%), with a further significant drop of 53% and 60% between baseline and after treatment, in the one- and two-tablet groups respectively ($p < 0.001$). A post-study analysis revealed abdominal pain/discomfort score reduced significantly by 22% and 25% in the one- and two-tablet group respectively, the difference tending toward significance ($p = 0.071$). There were significant improvements in all but one of the IBSQOL scales of between 5% and 36% in both groups, approximately two thirds of all subjects reported an improvement in symptoms after treatment, and there was a favorable shift in self-reported bowel pattern. There were no significant differences between groups. CONCLUSIONS: Turmeric may help reduce IBS symptomology. Placebo controlled trials are now warranted to confirm these findings.

26. The herbal preparation STW5 (Iberogast) has potent and region-specific effects on gastric motility.

Hohenester B, Ruehl A, Kelber O, Schemann M

Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society, 2004, 16 (6), 765-73.

Functional dyspepsia (FD) is amongst the most common functional gastrointestinal disorders. Symptomatic treatment includes the use of herbal preparations whose effects on gastric motility are unclear. The present study aimed at investigating the effects of STW 5 (Iberogast), a fixed combination of hydroethanolic herbal extracts, on gastric motility in vitro. Muscle strips from guinea-pig gastric fundus, corpus and antrum were set up in organ baths either in circular or longitudinal orientation. Addition of ethanol-free STW 5 to the organ baths (32-512 microg mL(-1)) dose-dependently evoked a sustained and reversible relaxation of circular and longitudinal fundus and corpus muscle strips without changes in phasic activity. In contrast, antral muscle strips responded to STW 5 with a significant increase in the contractile force of phasic contractions without changes in tone. All effects were resistant to tetrodotoxin (0.5 micromol L(-1)), atropine (1 micromol L(-1)), omega-conotoxin GVIA (0.5 micromol L(-1)), capsaicin (1 micromol L(-1)) or L-NAME (100 micromol L(-1)), suggesting that neither nerves nor nitric oxide pathways were involved. These data demonstrate that STW 5 profoundly alters gastric motility in a region-specific but not layer-specific manner and thus implicates Iberogast in the treatment of FD patients suffering from motility disorders with impaired fundus accommodation and/or antral hypomotility.

27. Basal and stimulated hypothalamic-pituitary-adrenal axis activity in patients with functional gastrointestinal disorders and healthy controls.

Boehmelt AH, Nater UM, Franke S, Hellhammer DH, Ehler U

Psychosomatic Medicine, 2005, 67 (2), 288-294.

OBJECTIVE: The aim of this study was to investigate alterations of pituitary-adrenal activity under both stimulated and unstimulated conditions in patients with functional gastrointestinal disorders. Methods: Thirty subjects who fulfilled the Rome Diagnostic Criteria for either irritable bowel syndrome or nonulcer dyspepsia and 24 healthy controls took part in the study. Free salivary morning cortisol and diurnal cortisol profiles were obtained for all subjects. On a second day, a low-dose dexamethasone suppression test was applied. Additionally, in all subjects a corticotropin-releasing hormone (CRH) challenge test was performed. Results: The results show attenuated unstimulated cortisol levels in patients compared with controls. After CRH challenge, blunted adrenocorticotropic hormone and cortisol responses were observed. These findings suggest lower pituitary and adrenocortical activity in patients with functional gastrointestinal disorders. Conclusion: The observed pituitary-adrenal reactivity in these patients is discussed as a possible consequence of lower adrenocortical activity, possibly resulting in a disinhibition of CRH in the brain. Copyright (C) 2005 by the American Psychosomatic Society.

28. Central cholecystokinin activity in irritable bowel syndrome, panic disorder, and healthy controls.

Koszycki D, Torres S, Swain JE, Bradwejn J

Psychosomatic Medicine, 2005, 67 (4), 590-595.

OBJECTIVE: Irritable bowel syndrome (IBS) and panic disorder (PD) coexist with a high frequency. However, the nature of this relationship remains obscure. We have proposed that PD and IBS may share a common dysfunction of the central cholecystokinin (CCK) system. To test this hypothesis, we assessed whether the enhanced panicogenic response to CCK-tetrapeptide (CCK-4) observed in PD is also present in IBS. Methods: Eight psychiatrically healthy IBS patients, 8 PD patients with no history of IBS, and 12 normal controls received a bolus injection of CCK-4 and placebo on two separate days in a double-blind, randomized fashion. Results: Consistent with previous findings, panicogenic sensitivity to CCK-4 was enhanced in PD patients relative to controls. In contrast, IBS patients exhibited a response that was comparable to controls. Interestingly, CCK-4-induced nausea and abdominal distress were decreased in IBS patients relative to the other groups.



No diagnostic difference was noted for cardiovascular response to CCK-4. Conclusion: These data indicate that IBS patients with no lifetime psychiatric history do not share the CCK-2 receptor dysfunction implicated in the pathophysiology of PD and that this dysfunction may not be a common mechanism for both CNS and enteric nervous system disorders. Nevertheless, the results suggest that a dysfunction of the CCK system may be involved in the pathophysiology of some enteric symptoms associated with IBS. Copyright (C) 2005 by the American Psychosomatic Society.

29. Role of progesterone signaling in the regulation of G-protein levels in female chronic constipation.

Xiao ZL, Pricolo V, Biancani P, Behar J
Gastroenterology, 2005, 128 (3), 667-75.

BACKGROUND & AIMS: Chronic constipation caused by slow transit is common in women with an F/M ratio of 9:1. The cause and mechanisms responsible for this syndrome are unknown. Progesterone has been suggested as a possible contributing factor. Our aim was to investigate the site and mechanisms responsible for this colonic motility disorder. METHODS: Seven women with intractable constipation and slow transit time underwent colectomy and 6 women who underwent a left colectomy for adenocarcinoma (controls) were studied. Dissociated colonic circular muscle cells were obtained by enzymatic digestion. Changes in G-protein levels were measured by Western blot. The messenger RNA (mRNA) expression of Galpha q and progesterone receptors was determined by reverse-transcription polymerase chain reaction and Northern blot. RESULTS: Muscle cells from patients with chronic constipation exhibited impaired contraction in response to receptor-G-protein-dependent agonists (cholecystokinin [CCK], acetylcholine) and in response to the direct G-protein activator guanosine 5'-O-(3-thiophosphate). Contraction was normal with receptor-G-protein-independent agonists (diacylglycerol and KCl). Western blot showed down-regulation of Galpha q/11 and up-regulation of Galpha s proteins in patients with chronic constipation. The mRNA expression of Galpha q was lower and the progesterone receptors were overexpressed in patients with chronic constipation compared with controls. These abnormalities were reproduced in vitro by pretreatment of normal colonic muscle cells with progesterone for 4 hours. CONCLUSIONS: Slow transit chronic constipation in women may be caused by down-regulation of contractile G proteins and up-regulation of inhibitory G proteins, probably caused by overexpression of progesterone receptors.

30. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario.

Marshall JK, Thabane M, Garg AX, Clark W, Meddings J, Collins SM
Alimentary pharmacology & therapeutics, 2004, 20 (11-12), 1317-22.

BACKGROUND: Post-infectious irritable bowel syndrome is a common clinical phenomenon of uncertain aetiology. AIM: To test the association between intestinal permeability and irritable bowel syndrome symptoms 2 years after a large waterborne outbreak of bacterial gastroenteritis. METHODS: Consecutive adults with Rome I irritable bowel syndrome and controls without irritable bowel syndrome attending a community clinic were enrolled. Intestinal permeability was measured as the ratio of fractional urinary excretions of lactulose and mannitol, and compared among cases vs. controls and predictors of abnormal intestinal permeability were assessed. RESULTS: A total of 218 subjects (132 irritable bowel syndrome cases and 86 non-irritable bowel syndrome controls) completed the study protocol. About 27 (12%) had been diagnosed with the irritable bowel syndrome before the outbreak and 115 (53%) had been ill during the outbreak. Lactulose-mannitol ratios were increased among cases vs. controls (Mann-Whitney mean rank 118.8 vs. 95.3, $P = 0.007$), and cases were more likely to have a ratio >0.020 ($P = 0.007$). Among cases, those with increased intestinal permeability were more likely to report increased stool frequency. Both irritable bowel syndrome symptoms and male gender, but not diarrhoeal illness during the outbreak, were significant predictors of abnormal permeability. CONCLUSIONS: Irritable bowel syndrome symptoms are associated with a subtle increase in intestinal permeability irrespective of prior gastroenteritis. This may improve understanding of the aetiology of both sporadic and post-infectious irritable bowel syndrome.

31. Plasma acylated ghrelin levels correlate with subjective symptoms of functional dyspepsia in female patients.

Shinomiya T, Fukunaga M, Akamizu T, Irako T, Yokode M, Kangawa K, Nakai Y, Nakai Y
Scandinavian journal of gastroenterology, 2005, 40 (6), 648-53.

OBJECTIVE: Ghrelin is a brain-gut peptide that is mainly secreted from gastric endocrine cells (X/A like cells). In addition to promoting growth-hormone release and appetite, ghrelin also affects gastric motility and secretion. Circulating ghrelin levels are related to appetite and energy



balance. Functional dyspepsia (FD) is a disorder characterized by the presence of chronic or recurrent symptoms of upper abdominal pain or discomfort. Although no known specific organic abnormalities are present in FD, abnormalities in gastrointestinal motility and sensitivity are thought to play a role in a substantial subgroup of patients. In addition, some patients also suffer from anorexia and body-weight loss. To investigate the role of ghrelin in the pathophysiology of FD, circulating ghrelin levels in affected patients were measured. **MATERIAL AND METHODS:** Eighteen Japanese female patients with functional dyspepsia and 18 healthy volunteers were recruited for the study. Acylated and desacyl forms of ghrelin were measured using commercially available enzyme-linked immunosorbent assay kits. **RESULTS:** Although plasma levels of acylated or desacyl ghrelin were not significantly different between healthy subjects and FD patients, plasma acylated, but not desacyl ghrelin, levels were correlated with a subjective symptom score in FD patients. In addition, the ratio of acylated to desacyl ghrelin (A/D ratio) was correlated strongly with acylated, but not desacyl, ghrelin levels. **CONCLUSIONS:** The correlation of circulating acylated ghrelin levels with the subjective symptom score and the A/D ratio in FD patients suggest that acylated ghrelin may play a role in the pathophysiology of FD.

32. Are cardiac syndrome X, irritable bowel syndrome and reflex sympathetic dystrophy examples of lateral medullary ischaemic syndromes?

Syme P

Medical hypotheses, 2005, 65 (1), 145-8.

Altered pain appreciation and autonomic function are hallmarks of Cardiac syndrome X, Irritable bowel syndrome and Reflex sympathetic dystrophy. Both pain appreciation and autonomic function are controlled by the lateral medulla. This hypothesis proposes that lateral medullary ischaemia at a microvascular level is responsible for these syndromes and could also be linked to other conditions where autonomic dysfunction is a major feature such as late-onset asthma, type 2 diabetes and essential hypertension. Autonomic function is controlled by the nucleus tractus solitarius, which acts as the main visceros-afferent nucleus in the brain stem regulating vagal tone. It is particularly susceptible to ischaemia since it is highly metabolically active and lies in a medullary arterial watershed zone. The anatomical route of the vertebral artery through cervical vertebra makes it vulnerable to injury from whiplash with or without any genetic predisposition to atheroma formation. This could make microvascular occlusion commonplace and a plausible explanation for the above syndromes. Ischaemia rather than infarction occurs because of the excellent collateral blood

supply in the brainstem. In support of this hypothesis, a new Transcranial doppler ultrasonography arterial signal has been described called small vessel knock, the ultrasound signal of small vessel occlusion. Recent evidence has shown that ultrasound targeting of this signal in the vertebral artery improves clinical symptoms in these syndromes which supports this hypothesis. Two such cases are discussed.

33. Increased beta-adrenergic sensitivity correlates with visceral hypersensitivity in patients with constipation-predominant irritable bowel syndrome.

Jung HP, Rhee P-L, Hyun SK, Jun HL, Kim Y-H, Jae JK, Jong CR, Eun HK, Yu B-H

Digestive Diseases and Sciences, 2005, 50 (8), 1454-1460.

Autonomic imbalance has been proposed to be a pathophysiological factor for irritable bowel syndrome (IBS). The aim of this study was to assess beta-adrenergic abnormalities in IBS and to evaluate their relationship to visceral hypersensitivity and other symptoms of IBS patients. Sixteen IBS patients and 16 control subjects were recruited into this study. Participants were asked to complete a questionnaire regarding bowel symptoms, and in order to study beta-adrenergic sensitivity, isoproterenol stimulation tests were performed and visceral hypersensitivity was evaluated by barostat test. Results showed that beta-adrenergic activity and rectal sensitivity were more pronounced in IBS patients than in normal control patients ($P < 0.01$). Although both IBS subgroups also exhibited more pronounced beta-adrenergic sensitivity than did the controls ($P < 0.05$), a significant correlation between beta-adrenergic activity and maximally tolerable pressures on the barostat test was found only in IBS-C patients ($P = 0.03$, $R = 0.855$). In addition, patients with "hard or lumpy" stools exhibited a higher degree of beta-adrenergic activity ($P = 0.00$). We conclude that increased beta-adrenergic activity significantly correlated with visceral hypersensitivity in constipation-predominant IBS and symptoms of hard or lumpy stools in IBS patients. (C) 2005 Springer Science+Business Media, Inc.

34. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome.

Zar S, Mincher L, Benson MJ, Kumar D

Scandinavian Journal of Gastroenterology, 2005, 40 (7), 800-807.

OBJECTIVE: Dietary modification improves symptoms in irritable bowel syndrome (IBS). Identification of offending foods by dietary elimination/re-challenge is cumbersome. IgG4 antibodies to common food antigens are elevated in IBS. The aim of this article was to evaluate the effect of



exclusion diet based on IgG4 titres on IBS symptoms and rectal sensitivity and compliance. Material and methods. The study comprised 25 patients with IBS (3 M, 22 F, mean age 43 years, Rome II criteria). IgG4 titres to 16 foods (milk, eggs, cheese, wheat, rice, potatoes, chicken, beef, pork, lamb, soya bean, fish, shrimps, yeast, tomatoes and peanuts) were measured. Foods with titres >250 microg/l were excluded for 6 months. Symptom severity was assessed with a previously validated questionnaire at baseline, at 3 months and at 6 months. Rectal compliance and sensitivity were measured in 12 patients at baseline and at 6 months. Results. IgG4 antibodies to milk, eggs, wheat, beef, pork and lamb were commonly elevated. Significant improvement was reported in pain severity ($p < 0.001$), pain frequency ($p = 0.034$), bloating severity ($p = 0.001$), satisfaction with bowel habits ($p = 0.004$) and effect of IBS on life in general ($p = 0.008$) at 3 months. Symptom improvement was maintained at 6 months. Rectal compliance was significantly increased ($p = 0.011$) at 6 months but the thresholds for urge to defecate/discomfort were unchanged. Conclusions. Food-specific IgG4 antibody-guided exclusion diet improves symptoms in IBS and is associated with an improvement in rectal compliance. (C) 2005 Taylor & Francis.

35. Rectal hyposensitivity: a disorder of the rectal wall or the afferent pathway? An assessment using the barostat.

Gladman MA, Dvorkin LS, Lunniss PJ, Williams NS, Scott SM
The American journal of gastroenterology, 2005, 100 (1), 106-14.

OBJECTIVES: Rectal hyposensitivity (RH) relates to a diminished perception of rectal distension. Diagnosis on the basis of abnormal threshold volumes on balloon distension alone may be inaccurate due to the influence of differing rectal wall properties. The aim of this study was to investigate whether RH was actually due to impaired afferent nerve function or whether it could be secondary to abnormalities of the rectal wall. METHODS: A total of 50 patients were referred consecutively to a tertiary referral unit for physiologic assessment of constipation (Rome II criteria), 25 of whom had associated fecal incontinence. Thirty patients had RH (elevated threshold volumes on latex balloon distension), and 20 patients had normal rectal sensation (NS). Results were compared with those obtained in 20 healthy volunteers (HV). All subjects underwent standard anorectal physiologic investigation, and assessment of rectal compliance, adaptive response to isobaric distension at urge threshold, and postprandial rectal response, using an electromechanical barostat. RESULTS: Mean rectal compliance was significantly elevated in patients with RH compared to NS and HV ($p < 0.001$).

However, 16 patients with RH (53%) had normal compliance. Intensity of the urge to defecate during random phasic isobaric distensions was significantly reduced in patients with RH compared to NS and HV ($p < 0.001$). The adaptive response at urge threshold was reduced in patients with RH compared to NS and HV ($p < 0.001$), although spontaneous adaptation at operating pressure was similar in all three groups studied ($p = 0.3$). Postprandially, responses were similar between groups. CONCLUSIONS: In patients found to have RH on simple balloon distension, impaired perception of rectal distension may be partly explained in one subgroup by abnormal rectal compliance. However, a second subgroup exists with normal rectal wall properties, suggestive of a true impairment of the afferent pathway. The barostat has an important role in the identification of these subgroups of patients.

36. Effect of acute physical and psychological stress on gut autonomic innervation in irritable bowel syndrome.

Murray CD, Flynn J, Ratcliffe L, Jacyna MR, Kamm MA, Emmanuel AV
Gastroenterology, 2004, 127 (6), 1695-703.

BACKGROUND & AIMS: Stress is an important causative factor in irritable bowel syndrome (IBS). It remains unknown whether stress-related changes in gut function are mediated by altered autonomic efferent gut-specific innervation. We studied the effect of acute physical and psychological stress on autonomic innervation and visceral sensitivity in healthy volunteers and patients with IBS. METHODS: Twenty-four patients (20 women) with constipation-predominant IBS and 12 healthy volunteers (8 women) underwent either physical (cold water hand immersion) or psychological (dichotomous listening) stress on separate occasions. Assessments included stress perception (visual analogue scale), gut-specific autonomic innervation (rectal mucosal blood flow [RMBF] by laser Doppler flowmetry), and viscerosomatic sensitivity (anal and rectal electro-sensitivity). RESULTS: Patients with IBS had a heightened baseline perception of stress ($P < .01$). RMBF decreased during physical stress (29.6% +/- 2.8% and 28.7% +/- 3.9%) and psychological stress (24.4% +/- 2.1% and 23.5% +/- 4.3%) in patients with IBS and controls, respectively (mean +/- SEM). During physical stress, rectal perception (23.2% +/- 6% vs .6% +/- 3% [IBS vs control group, $P < .05$]) and rectal pain thresholds (27.0% +/- 4% vs 1.3% +/- 5%, $P < .001$) decreased in patients with IBS only. Psychological stress reduced thresholds for rectal perception (19.4% +/- 6% vs 8% +/- 6%, $P < .01$) and rectal pain (28.4% +/- 4% vs 3.4% +/- 3.8%, $P < .001$) in patients with IBS only. Acute stress elevated anal perception thresholds in patients with IBS but not controls (physical stress: 14.7% +/- 14% vs -9.3% +/- 11%, $P < .05$;



psychological stress: 24.7% +/- 9% vs 11% +/- 11%, $P < .05$). **CONCLUSIONS:** Acute stress alters gut-specific efferent autonomic innervation in both controls and patients with IBS, although normalization is delayed in IBS. By contrast, only patients with IBS show heightened visceral sensation, suggesting involvement of a different regulatory mechanism, either central or peripheral.

37. Psychophysical evidence of hypersensitivity in subjects with interstitial cystitis.

Ness TJ, Powell-Boone T, Cannon R, Lloyd LK, Fillingim RB
The Journal of urology, 2005, 173 (6), 1983-7.

PURPOSE: We quantified differences in somatic and visceral sensation in healthy subjects and subjects with interstitial cystitis (IC). **MATERIALS AND METHODS:** A total of 13 subjects with IC and 13 healthy subjects answered psychological questionnaires and underwent psychophysical testing of thermal and pressure thresholds for sensation as well as the ischemic forearm test of pain tolerance. A subset of subjects also underwent bladder sensory testing with the determination of 3 consecutive cystometrograms. Ratings of intensity and unpleasantness were determined. **RESULTS:** Subjects with IC were significantly more sensitive to deep tissue measures of sensation related to pressure, ischemia and bladder than healthy subjects. Cutaneous thermal pain measures were similar in the 2 groups. Psychological measures indicated higher reactivity in subjects with IC. **CONCLUSIONS:** Similar to other visceral pain disorders, such as irritable bowel syndrome, hypersensitivity to somatic stimuli was noted in subjects with IC. This suggests altered central mechanisms in the processing of sensory events from the bladder.

38. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome.

Morgan V, Pickens D, Gautam S, Kessler R, Mertz H
Gut, 2005, 54 (5), 601-7.

BACKGROUND AND AIMS: Irritable bowel syndrome (IBS) is a disorder of intestinal hypersensitivity and altered motility, exacerbated by stress. Functional magnetic resonance imaging (fMRI) during painful rectal distension in IBS has demonstrated greater activation of the anterior cingulate cortex (ACC), an area relevant to pain and emotions. Tricyclic antidepressants are effective for IBS. The aim of this study was to determine if low dose amitriptyline reduces ACC activation during painful rectal distension in IBS to confer clinical benefits. Secondary aims were to identify other brain regions altered by amitriptyline, and to determine if reductions in cerebral activation are greater

during mental stress. **METHODS:** Nineteen women with painful IBS were randomised to amitriptyline 50 mg or placebo for one month and then crossed over to the alternate treatment after washout. Cerebral activation during rectal distension was compared between placebo and amitriptyline groups by fMRI. Distensions were performed alternately during auditory stress and relaxing music. **RESULTS:** Rectal pain induced significant activation of the perigenual ACC, right insula, and right prefrontal cortex. Amitriptyline was associated with reduced pain related cerebral activations in the perigenual ACC and the left posterior parietal cortex, but only during stress. **CONCLUSIONS:** The tricyclic antidepressant amitriptyline reduces brain activation during pain in the perigenual (limbic) anterior cingulate cortex and parietal association cortex. These reductions are only seen during stress. Amitriptyline is likely to work in the central nervous system rather than peripherally to blunt pain and other symptoms exacerbated by stress in IBS.

39. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis.

Mayer EA, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, Chang L
Pain, 2005, 115 (3), 398-409.

Patients with mild chronic inflammation of the rectum or ileum have reduced perceptual responses to rectosigmoid distension compared to patients with irritable bowel syndrome (IBS). The current study sought to identify differences in regional cerebral blood flow (rCBF) during rectal distension, which might correspond to these perceptual differences. In 8 male ulcerative colitis (UC) patients with quiescent disease, 7 male IBS patients and 7 healthy male controls, rCBF was assessed using 15O-water positron emission tomography at baseline and during actual and anticipated but undelivered rectal distensions. No group differences were seen in anterior insula and dorsal anterior cingulate cortex (dACC), two regions consistently activated by painful intestinal stimuli. However, IBS patients showed greater activation of the amygdala, rostroventral ACC, and dorsomedial frontal cortical regions. In contrast, no significant differences were observed between UC and controls. When these two non-IBS groups were combined, functional connectivity analyses showed that right lateral frontal cortex (RLFC) activation positively correlated with activation of the dorsal pons/periaqueductal gray, a key region involved in endogenous pain inhibition. According to the connectivity analysis, this effect was mediated by inhibition of medial frontal cortex by the RLFC. Chronic colonic inflammation is not necessarily associated with



increased visceral afferent input to the brain during rectal distension. In the sample studied, the primary difference between functional and quiescent inflammatory disease of the colon was in terms of greater activation of limbic/paralimbic circuits in IBS, and inhibition of these circuits in UC and controls by the RLFC.

40. Irritable bowel syndrome: the commonest cause of recurrent abdominal pain in children.

El-Matary W, Spray C, Sandhu B
European journal of pediatrics, 2004, 163 (10), 584-8.

Apley, working in Bristol, UK, defined recurrent abdominal pain (RAP) in 1958. After extensive investigations, he found that 8% of children presenting to his clinic with RAP had an organic pathology. The aims of this study were to identify (1) causes of RAP using modern methodology, (2) factors associated with organic RAP and (3) children with non-organic RAP who fulfill the diagnostic criteria for irritable bowel syndrome (IBS). Children, aged over 3 years, presenting with RAP were prospectively recruited to this study. They had a detailed questionnaire completed, a full examination with screening tests (blood for coeliac screen, Helicobacter pylori antibody titre, inflammatory markers, serum amylase, liver function tests, and full blood count, urine and stool analyses and abdominal ultrasonography). Endoscopy and oesophageal pH monitoring were performed if clinically indicated. IBS was diagnosed if the child had no organic pathology and fulfilled the Rome II criteria. Out of 103 children (median age of 10 years, mean 10.04, SD +/- 3.44), 31 children (30%) had organic pathologies. Factors associated with organic pain were nocturnal symptoms ($P < 0.01$) and abdominal tenderness ($P < 0.005$) and with non-organic pain were periumbilical locality ($P < 0.002$), pain alleviation on defaecation ($P < 0.04$) and low fibre diet ($P < 0.005$). Of children with non-organic pain, 37/52 (51%) fulfilled the criteria for IBS (36% of the total). Conclusion: Of children presenting with recurrent abdominal pain in a hospital setting, 30% have a diagnosable organic aetiology compared to 8% in Apley's time. Irritable bowel syndrome, however, may be the commonest cause of recurrent abdominal pain and should be considered.

41. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms.

Levy RL, Whitehead WE, Walker LS, Von Korff M, Feld AD, Garner M, Christie D
The American journal of gastroenterology, 2004, 99 (12), 2442-51.

OBJECTIVES: Irritable bowel syndrome (IBS) runs in families. The aims of this study were (i) to exclude biased perception by a mother with irritable bowel as the explanation for increased gastrointestinal (GI) symptoms in their children, (ii) to determine whether non-GI as well as GI symptoms run in families, and (iii) to determine whether parent IBS status and solicitous responses to illness exert independent effects on children's symptom reports, medical clinic visits, and school absences. **METHODS:** Two hundred and eight mothers with irritable bowel and their 296 children (cases: average age 11.9 yr; 48.6% male) and 241 nonirritable bowel mothers and their 335 children (controls: 11.8 yr; 49.0% male) were interviewed. Other factors assessed were stress, mother's and child's psychological symptoms, child's perceived competence, pain coping style, age, and sex. Children were interviewed apart from their parents. **RESULTS:** Case children independently reported more frequent stomach aches ($F(591) = 9.22$; $p = 0.0025$) and non-GI symptoms ($F(562) = 21.03$; $p < 0.001$) than control children. Case children also had more school absences ($F(625) = 26.53$; $p < 0.0001$), physician visits for GI symptoms ($F(602) = 8.09$; $p = 0.005$), and non-GI clinic visits ($F(602) = 27.92$; $p < 0.001$) than control children. Children whose mothers made solicitous responses to illness complaints independently reported more severe stomach aches ($F(590) = 11.42$; $p < 0.001$), and they also had more school absences for stomach aches ($F(625) = 5.33$; $p < 0.05$), but solicitous behavior did not significantly impact non-GI symptom reporting, clinic visits, or school absences. Differences between cases and controls remained significant after adjusting for potential moderators. **CONCLUSIONS:** (i) Frequent GI complaints in children whose mothers have irritable bowel are not explained by the mother's biased perceptions; (ii) children of mothers with irritable bowel have more non-GI as well as GI symptoms, disability days, and clinical visits; (iii) and parent IBS status and solicitous responses to illness have independent effects on the child's symptom complaints.

42. Recurrent abdominal pain in children revisited: irritable bowel syndrome and psychosomatic aspects.

A prospective study.
Nygaard EA, Stordal K, Bentsen BS
Scandinavian journal of gastroenterology, 2004, 39 (10), 938-40.

BACKGROUND: Since Apley, more than 40 years ago, concluded that less than 10% of cases with recurrent abdominal pain (RAP) are of organic origin, medical technology has improved, the knowledge has expanded and new methods of investigation have been developed. The



lack of organic findings in many children with RAP has led to the conclusion that psychological factors are important. **METHODS:** Forty-four children with RAP underwent an investigation programme to find organic abnormalities that might explain the symptoms. Current criteria for irritable bowel syndrome (IBS) in children were used to find out what proportion fulfilled these criteria, irrespective of the organic findings on clinical investigation. A standardized questionnaire, the CBCL (Child Behaviour Checklist), was used to evaluate emotional and behavioural disturbances in children referred for RAP. **RESULTS:** Thirteen out of 26 (50%) children with no signs of organic disease fulfilled the IBS criteria as opposed to 7 out of 18 (39%) children in the group with organic findings ($P = 0.68$). The total score for the CBCL was in the normal range for 32 out of 36 of the children. **CONCLUSIONS:** We found a high proportion of children fulfilling the IBS criteria in both groups, thus organic abnormalities have to be excluded before making the IBS diagnosis. The results of the CBCL forms did not show any difference between children with organic versus those with non-organic abnormalities, both groups within the normal range.

43. Effect of CCK-1 antagonist, dexloiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study.

Cremonini F, Camilleri M, McKinzie S, Carlson P, Camilleri CE, Burton D, Thomforde G, Urrutia R, Zinsmeister AR
The American journal of gastroenterology, 2005, 100 (3), 652-63.

BACKGROUND: Cholecystokinin (CCK) is involved in gastrointestinal motor response to meals. The potential role of CCK receptor antagonists in functional gastrointestinal disorders is unclear. **AIMS:** To evaluate the effects of dexloiglumide, a CCK-1 receptor antagonist, on gastrointestinal transit (GIT) and symptoms in patients with constipation-predominant IBS (C-IBS); and to explore the influence of CCK-1 receptor polymorphisms on gut transit and the pharmacodynamic response to therapy. **METHODS:** A total of 36 patients with C-IBS and normal to slow baseline colonic transit (CT) were randomized (double-blind, parallel design) to 7 days of dexloiglumide 200 mg or placebo t.i.d. Daily bowel habits diaries and weekly relief of IBS symptoms were recorded. At the end of treatment, GIT and CT were measured. Peripheral blood DNA was examined for polymorphisms in genes controlling CCK: four related to CCK-1, one to the CCK gene promoter, and one related to CCK-2. The distributions of allelic variants and association

with gastric emptying in response to dexloiglumide and placebo were assessed. **RESULTS:** Dexloiglumide was associated with accelerated gastric emptying $t(1/2)$ ($p = 0.004$), and slower ascending colon emptying $t(1/2)$ ($p < 0.01$), with no significant effect on overall CT or satisfactory relief of IBS. There was an association between CCK 779T > C polymorphism and slower rate of gastric emptying ($p = 0.04$). **CONCLUSIONS:** Dexloiglumide accelerates gastric emptying and delays proximal but not overall CT in patients with C-IBS. Dexloiglumide does not accelerate transit in C-IBS. The role of CCK-1 gene polymorphisms in delaying gastric emptying and in determining response to therapy deserves further study.

44. Genetic influences in irritable bowel syndrome: a twin study.

Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ
The American journal of gastroenterology, 2005, 100 (6), 1340-4.

BACKGROUND: Aggregation of symptoms of abdominal pain or bowel disturbance has been described in the families of patients with irritable bowel syndrome (IBS). This may be due to environmental factors, including learned responses to abdominal symptoms or a genetic contribution to the etiology of IBS. **OBJECTIVES:** To determine the relative contribution of genetic factors to IBS by evaluating IBS symptoms in monozygotic (MZ) and dizygotic (DZ) twins. **METHODS:** A total of 4,480 unselected twin pairs identified from a national volunteer twin register were asked to complete a validated questionnaire. IBS was defined by the Rome II criteria. **RESULTS:** A total of 5,032 subjects replied (56% response rate). One thousand eight hundred seventy complete twin pairs were evaluable; 888 MZ pairs (82 male pairs, mean age 51, SD 13 (range 19-81) yr) and 982 DZ pairs (69 male pairs, age 52, SD 13 (20-82) yr). The prevalence of IBS was 17% in MZ and 16% in DZ twins. There was no significant difference in casewise concordance rates between the MZ and DZ twins (28% vs 27%, $p = NS$). Logistic regression analysis revealed that decreasing age and increasing psychosomatic score were independently associated with IBS. Multifactorial liability threshold modeling suggested that a combination of unique and shared environmental factors provided the best model for IBS. In contrast, somatization was shown to be moderately heritable. **CONCLUSION:** Genetic factors are of little or no influence on IBS where the predominant influences appear to be environmental.