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Preface

Irritable Bowel Syndrome

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Guest Editor

The irritable bowel syndrome (IBS) remains an enigmatic condition that has come under much greater scrutiny in the past decade, leading to notable advances that are summarized in this issue of the *Gastroenterology Clinics of North America*.

There continues to be progress in refining the clinical definition of IBS; however, there are also controversies, as highlighted by Dr. Longstreth in his expert review of this topic. Although there is increasing evidence that IBS occurs worldwide, some intriguing data also exist suggesting that the condition is less common in Asia, which may reflect genetic or environmental factors. These and other issues in the epidemiology of IBS are reviewed by Dr. Cremonini and myself in this issue. The diagnosis of IBS has become much more straightforward, following recent emphasis on the futility of testing in the setting of a clear-cut history and the absence of any "red flags." Drs. Cash and Chey review the available data here, including the controversies surrounding celiac disease and IBS. The cause of IBS remains unclear, but disturbances of motility and visceral hypersensitivity are now well described. Dr. Quigley reviews the evidence for these abnormalities as possible biological markers in IBS. Of great interest is the hypothesis that some forms of IBS represent a low-grade inflammatory bowel disease. This seems more likely than ever, and Dr. Bercik and colleagues review the rapidly growing literature in this intriguing area. The role of food intolerance in IBS has been largely ignored, despite positive studies suggesting at least a subset of IBS patients truly will respond to elimination diets, as Drs. Lea and Whorwell discuss. Why does bloating

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commonly occur in IBS? This has been a perplexing question, but recent data support the view that there may be intestinal gas trapping and increased gas producing intestinal flora, as reviewed by Drs. Azpiroz and Malagelada. Many patients with IBS have symptoms outside the intestinal tract, leading some to believe that this may be a disease of the brain rather than the gut. Dr. Chang tackles this important area, reviewing the latest work on brain imaging in IBS. The role of psychiatric and psychologic dysfunction in IBS continues to be debated, although there is no doubt they contribute to its morbidity, as reviewed by Drs. Pallson and Drossman. Intense interest currently surrounds the potential role of genes in IBS, and this topic is reviewed by Drs. Park and Camilleri. The number of candidate genes potentially linked to IBS continues to grow, and research here may change the field. The treatment of IBS remains challenging, and indeed the evidence base for current therapies is more limited than some appreciate, as reviewed by Dr. Schoenfeld. Finally, Dr. Spiller considers potential future therapies for IBS, including approaches to disease modification.

It is very pleasing to have been able to gather the current world authorities in the field to review the state-of-the-art in IBS. It seems more likely than ever that at least a subset of patients with IBS truly have structural disease; current research has the promise of leading to more efficacious treatments for those who suffer with this affliction.

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Definition and Classification of Irritable Bowel Syndrome: Current Consensus and Controversies

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> "The diagnosis of disease is often easy, often difficult, and often impossible."
>
> Peter Mere Latham (1789–1875) [1]

Irritable bowel syndrome (IBS), the prototypical functional gastrointestinal (GI) disorder, is common throughout the world and often requires care from primary care and specialist physicians. Because no etiology is found with routine diagnostic testing, IBS is a symptom-based diagnosis, requiring chronic abdominal discomfort or pain and abnormal bowel function; other GI symptoms are also common. Over 150 years ago, the heterogeneity of symptoms puzzled Cumming who wrote "The bowels are at one time constipated, another lax, in the same person.... How the disease has two such different symptoms I do not profess to explain" [2]. An important case series was described in 1961 [3], and research on the diagnosis of IBS has surged during the past 20 years. Although there is consensus among many physicians on the definition and classification of IBS, other experts' opinions are as disparate as those expressed in the opening quotation.

IBS appears to be part of a continuum of GI and central nervous system (CNS) reactions to external and internal stimuli. At one end of this spectrum, many people have functional GI symptoms in response to emotional stress. Of health examinees, 51% of females and 29% of males 14 to 44 years of age reported a stress effect on bowel pattern, and 36% of females and 13% of males in this age group reported a stress effect on abdominal pain. Both stress effects declined with age in both sexes [4].

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Many such individuals do not seek health care for these symptoms, yet others have severe symptoms with or without stress that impair their quality of life. In the absence of a biological marker, defining abnormality on the spectrum ranging from occasional, stress-related GI symptoms in people not seeking care to disabling symptoms in patients with refractory IBS is controversial.

Definitions

Disease, disorder, syndrome, illness, functional, or organic?

The Rome II working team defined IBS as "a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit and with features of disordered defecation" [5,6]. IBS meets dictionary definitions of disease, disorder, and syndrome [7–9]. The word disorder, however, sometimes is applied when function is altered without morphological change, often implying unknown or psychological causes [10], leaving disease for entities with an organic (structural) abnormality. Illness is a broader concept that differs from physicians' biomedical disease concept and embodies a sick person's experience, so regardless of whether the term disease or disorder is used, illness applies from the patient's perspective.

Recent research advances have generated controversy about whether IBS is functional or organic. Perturbations of the neuroendocrine control of GI function led Mayer to regard the traditional separation of functional and organic categories as obsolete [11], and Talley and Spillar cited abnormal brain activation by painful stimuli, subtle intestinal inflammation, and other evolving concepts of pathophysiology to consider IBS "a discrete collection of organic bowel diseases" [12]. Regardless of whatever importance is associated with IBS terminology, Drossman cautioned against allowing the organification of IBS to focus diagnostic and therapeutic efforts excessively on specific pathophysiological aspects at the expense of more comprehensive, biopsychosocial management [13].

A multi-national group recently excluded IBS from a motility-based classification system of GI disorders, citing uncertainty that symptom groups reflect specific function alterations and discounting symptom-based diagnosis [14]. The new classification proposed the term enteric dysmotility for IBS. This taxonomy would require routine manometry, but motility testing rarely is done in patients with IBS, and it has not shown consistent abnormalities, so most IBS patients would have no classification. The discovery of manometric or other abnormalities that lead to improved treatment would be welcomed, but clustering of the Rome II symptoms in individuals indicates that IBS is a syndrome, and patients require symptom-based management [15].

Irritable bowel syndrome symptoms

Semantics in research and practice

The patient's history is paramount in diagnosis, but a symptom descriptor can mean different things to different people, and multiple terms can be applied to the same symptom, demanding interpretive skill from practitioners. Linguists recognize three types of word or statement meanings: (1) referential meaning of an object or concept; (2) social meaning that reflects a person's social class, ethnicity, regional origin, and context; and (3) affective meaning that expresses feelings and attitudes [16]. The multifactorial nature of language meaning can lead to disagreement among users of the same language about symptom terms and complicates attempts to standardize their meanings. In addition, patients can manifest many types of pathophysiology with only a few nociceptive sensations, making the correlation of symptoms with GI events and their CNS processing even more problematic.

Physicians must ask patients what they mean when they report a symptom to fully understand its referential meaning. For example, simply asking about constipation and diarrhea is insufficient. Constipation can mean straining (even to pass liquid stools [pseudoconstipation]), a sensation of incomplete evacuation, reduced frequency of evacuation, or lumpy stools. The latter alteration is associated with slow colonic transit [17]. Diarrhea, the passage of mushy or liquid stools, should be differentiated from pseudodiarrhea, which is frequent defecation and urgency with solid stools, as true diarrhea is associated with rapid transit [18]. Patients often report an alternating bowel habit. Some say that after an episode of diarrhea they pass no stool for a few days before again evacuating loose stools. Although such patients may describe the intervening period as constipation, it could merely represent a period when the colon contains little stool, and sequential transit studies on patients with this history could be worthwhile. Use of the pictorial Bristol stool form scale is a convenient method of classifying stool form that can be used to estimate GI transit [19].

Abdominal discomfort can be interpreted by patients either as a lower intensity of the same nociceptive sensation as pain or as a qualitatively different, unpleasant feeling that may include fullness, early satiety, bloating, and nausea [20]. Whether different meanings of discomfort and pain affect the accuracy of diagnosing IBS is unknown. Bloating is defined as both abdominal distension [7–9] and tympany [7], depending on the source. Moreover, patients do not associate bloating uniformly with distension and may report it with borborygmns, excessive flatus, and frequent eructation. Chang et al suggested that the sensation of bloating is related to visceral hypersensitivity and that visible abdominal distension is caused by abdominal wall muscle hypotonia [21]. More research is needed, preferably with objective measurement of distension [22]. Bloating is also

common in functional constipation, functional dyspepsia, and premenstrual syndrome [23]. Gas is so ambiguous that further explanation is required, as it can represent eructation, bloating, flatus, heartburn, discomfort, or pain. Thompson and Heaton have suggested specific questions that can help physicians obtain the history [24]. Importantly, there is a paucity of cross-cultural comparison data on the meanings of symptom terms in different societies. Some languages lack a word for some English terms (eg, bloating).

Chronic pelvic pain has special clinical importance. Gynecologists apply the word pelvic (relating to the pelvis, a bony structure) to soft tissue organs within the pelvic cavity and pain originating in them [25]. Pain that gynecologists call pelvic may be abdominal to gastroenterologists, an example of artifactual symptom attribution caused by specialization [26]. A danger of specialist-biased terminology is that use of the word pelvic to describe IBS pain could focus medical attention excessively on gynecological organs. The association of gynecological symptoms with IBS, menstrual worsening of IBS symptoms, and higher rates of psychopathology in women diagnosed to have chronic pelvic pain and IBS than in women with IBS alone [27,28] could contribute to the predisposition of women with IBS to undergo hysterectomy. Misdiagnosis of the etiology of pain could be an important factor. Hysterectomy rates were 33.2% and 17.0% in health examinees with and without physician-diagnosed IBS, respectively. Among numerous variables tested, the adjusted odds ratio for the independent association of IBS with hysterectomy (1.70) nearly tied with fibromyalgia and black race for the highest value. Mistaken symptom attribution also could account for the threefold increase in cholecystectomy rate and twofold increase in appendectomy rate reported by examinees with IBS [29].

Evolution of symptom criteria

A small but influential study reported by Manning et al in 1978 [30] revealed that three pain-related symptoms (pain eased after a bowel movement, looser stools at onset of pain, and more frequent bowel movements at onset of pain) and abdominal distension differentiated patients with IBS from those with organic disease. In addition, mucus per rectum and feeling of incomplete evacuation did not differ individually in frequency between the groups, but discrimination increased when these two symptoms were combined with the other four symptoms. A decade later, a working team developed guidelines for diagnosing IBS [31]. Subsequently, authorities published a classification system for 21 functional GI disorders [32]. Additional multi-national work led to the Rome criteria for IBS by consensus, beginning with the Rome I criteria, the first symptom guidelines to require chronic abdominal pain [33,34]. A new working team considered research advances, particularly the results of factor analyses [35,36], and revised the diagnostic symptoms, yielding the Rome II criteria (Box 1) [5,6,37]. These criteria retain the three pain-related Manning symptoms,

Box 1. Rome II diagnostic criteria for irritable bowel syndrome

At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

- Relieved with defecation and/or
- Onset associated with a change in frequency of stool and/or
- Onset associated with a change in form (appearance) of stool

Symptoms that cumulatively support the diagnosis of irritable bowel syndrome

- Abnormal stool frequency (for research purposes abnormal may be defined as greater than three bowel movements per day and less than three bowel movements per week)
- Abnormal stool form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

From Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disease and functional abdominal pain. Gut 1999;45(Suppl 2):43–7; with permission.

because they clustered in factor analyses, and consign mucus and abdominal distension/bloating to nonessential but supportive criteria because of their poor clustering with other symptoms and lower prevalence in men [38]. There are separate Rome II criteria for functional abdominal bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder. The Rome III criteria are being developed, and the initial report will appear in early 2006.

Some supportive symptoms (evacuation frequency, stool form, and straining or urgency) were suggested to further classify IBS by the predominant bowel habit [5,6], and this scheme has been used to define entry criteria for patients enrolling in therapeutic trials for constipation- or diarrhea-predominant IBS. The validity of this classification, however, is controversial. Mearin et al found in a random population survey that there was poor correlation between self-reported constipation and diarrhea and the corresponding stool frequency criteria of the subtyping scheme. For example, patients who pass four hard stools daily (''pseudodiarrhea'') would be classified as having a mixed pattern even if they report constipation [39]. Thus, the stool form, which can serve to estimate transit [19], could be a better guide than evacuation frequency to motility-active, pharmacological therapy.

Separation of constipation-predominant IBS from functional constipation has challenged the Rome working teams. The functional constipation

criteria encompass symptoms associated with both delayed transit and defecation dysfunction [5,6], but they do not include abdominal discomfort or pain. Nevertheless, constipated patients often report at least mild discomfort that is relieved after defecation. There is no authoritative definition for the threshold of discomfort that should distinguish these two disorders in such patients. Rather, the separation is a subjective physician judgment.

Investigators have used the Manning, Rome I and Rome II and other criteria to estimate the prevalence of IBS. Because IBS is much more prevalent than organic disease, in population-based surveys the chance of erroneously labeling individuals who have organic disease is small, and some surveys have excluded subjects with known organic disease to further minimize this risk. The symptom criteria, however, never have been promoted as the sole diagnostic tool in clinical practice. Their use in patient management should be accompanied by additional history and an individualized diagnostic evaluation, often requiring only limited testing [40,41]. Because IBS is so common, it can coexist with organic GI disease. For example, one third of ulcerative colitis patients and 42% of Crohn's disease patients whose inflammatory bowel disease was in remission had IBS-like symptoms [42].

Extraintestinal somatic conditions (eg, fibromyalgia and chronic fatigue syndrome), symptoms (eg, headache and insomnia), and psychiatric disorders (eg, depression and anxiety) occur frequently in referred patients, but they seem to be distinct disorders and are not included in the IBS diagnostic criteria. Multiple comorbid disorders may be a marker for psychological contributions to IBS [43].

Some researchers have reported that non-GI symptoms have special associations. For example, Schmulson et al found that patients with constipation-predominant IBS have greater musculoskeletal symptoms; sleep disturbance; more frequent lower gut symptoms; and more frequent bloating, fullness, and satiety than patients with diarrhea-predominant IBS [44]. Guthrie et al have identified three groups of referred patients with severe IBS by cluster analysis of rectal distension perception thresholds, psychological parameters, physician consulting frequency, and bowel symptom type [45]. Because visceral sensitivity measurement is required, this method of classification is unlikely to be applied to many patients, but it could be used to characterize subjects for treatment trials.

Duration/frequency criteria

An acute episode of abdominal pain with bowel habit change (eg, acute gastroenteritis) should be distinguished from similar but chronic symptoms, just as occasional, stress-related symptoms should not necessarily be medicalized into a chronic syndrome [46]. The Rome I criteria require "at least 3 months of continuous or recurrent symptoms" [33,34], whereas the

Rome II criteria include more complex duration/frequency criteria during 12 months (see Box 1). Because this duration/frequency part of the Rome II criteria is rather impracticable, the Rome II Coordinating Committee shortened the duration and simplified this section on the modular research questionnaire to: "In the last 3 months, did you often have discomfort or pain in your abdomen? [47]. Arbitrariness is present in these criteria. Various duration/frequency criteria could influence population prevalence rates, and judgment must apply to their use in clinical practice.

Research with symptom criteria

Natural history and subtype durability

IBS is a chronic disorder that is expected to come and go and vary in severity. Importantly, once IBS has been identified correctly, the diagnosis holds up over the long term. For example, a review of six clinic-based studies revealed that during 6 months to 6 years of follow-up only 2% to 5% of patients were diagnosed with an alternative organic disease. In many cases, the new disease was unlikely to have caused the IBS symptoms years before (eg, gastric ulcer and pancreatic cancer) [48]. Although a population-based study showed transition of IBS to dyspepsia and gastroesophageal reflux disease [49], there are scarce data on the interchange of functional disorders over time among clinic patients.

Management is determined often by the predominant symptom, and recently drugs have been designed specifically to alleviate diarrhea or constipation. Investigators have used the Rome II subtype scheme to evaluate drugs (eg, serotoninergic neuroenteric modulators), which has led to guidelines for their use by patients with a predominant bowl habit abnormality. The assumption that the predominant bowel disturbance would remain unchanged over the long term or even throughout a clinical trial is questionable, however. Diary recordings, which may be more accurate than recall [50], by 63 referred patients revealed a decline in the number of days with pain over 6 weeks, but there was little variation of stool form or frequency [50]. A 12-week diary study of 209 primary care patients, however, showed that between the initial and final 4-week periods, one third of subjects changed subtypes, primarily from a diarrhea- or constipation-predominant pattern to a mixed or alternating bowel pattern. Symptom intensity was also highly unstable [51]. These findings and other observations, including a tendency for the frequency and intensity of symptoms to increase in the late luteal and early menses phases [27], and the frequent finding of an alternating subtype among subjects with IBS identified in a population survey [39], indicate natural symptom instability. This uncertainty about the stability of the subtypes suggests that on-demand medication dosing might be more effective than regular dosing for many patients [51].

Criteria assessment and prevalence rates

Even though the Rome I and Rome II criteria were based on the Manning symptoms, differences among the three sets of criteria are great enough that they do not necessarily identify the same patients or survey subjects. The Manning symptoms specify no symptom duration, and the Rome I and Rome II criteria differ in duration/frequency criteria. The Rome I criteria require only one pain-related Manning symptom, but the Rome II criteria require two of them. A critical panel's review of publications through April 2000 revealed that the Manning symptoms had been evaluated most extensively [52]. Their sensitivity and specificity for diagnosing IBS depend on how many symptoms are required and whether only the four individually significant symptoms or all six symptoms are considered. In general, sensitivity increases and specificity decreases with increasing number of symptoms. In studies requiring three or more Manning symptoms (whether four or six were assessed), sensitivity ranged from 63% to 90%, and specificity varied from 70% to 93%. They have more accurately distinguished IBS patients from healthy controls than from patients with organic GI disease. Importantly, evaluation of Rome I criteria in referral patients who lacked alarm features (weight loss, nocturnal symptoms, blood mixed in the stools, recent antibiotic use, family history of colon cancer, and relevant abnormalities on physical examination) revealed a sensitivity of 65%, specificity of 100%, and positive predictive value of 98% [53]. After the panel review, a United States national survey of 1014 patients with an IBS diagnosis revealed sensitivities of 84% and 49% for Rome I and Rome II criteria [54].

Population surveys have revealed varying prevalence rates, depending on the criteria used [55]. Among epidemiological surveys that have identified IBS according to the Rome II criteria (and sometimes other criteria too), population demographics and research methodology and have varied widely (Table 1). Therefore, the variation in reported prevalence rates could be attributable to differences in region, survey method, subject response rate, proportion of females, number of Manning symptoms, and the duration/frequency criteria. Some surveys have extrapolated data from common duration/frequency and symptom questions to estimate prevalence rates by multiple sets of criteria, despite varied wording of the published criteria. In contrast, Mearin et al assessed multiple prevalence rates with duration/frequency criteria specific for each set of IBS criteria [56].

Usefulness of alarm features

Conventional wisdom holds that certain red flag alarm features should mandate especially thorough testing to exclude organic disease. Kruis et al devised an IBS diagnostic scoring system that consisted of features from the history, physical examination, and basic laboratory testing [57]. The score differentiated IBS from organic disease; however, hematochezia, which is

Table 1
Methodological, demographic and prevalence comparisons from population surveys using the Rome II criteria

Primary author	Survey summary and results
Boyce [69]	Australia (Pernith), population-based, self-report (mailed) questionnaire; 4500 contacted, 2910 (72%) respondents (52% female) Same questions for Manning (at least 2 symptoms), Rome I and Rome II criteria Pain and duration/frequency: "pain or discomfort in your abdomen, stomach or tummy?" ≥3 months, >25% of the time Prevalence (%): Manning (13.6), Rome I (4.4), Rome II (6.9)
Mearin [56]	Spain, random, self-report (face-to-face) questionnaire; 2000 contacted; of 281 with positive screen 213 (76%; 51% female) gave complete data. Statistical correction for incomplete data group Pain and duration/frequency: initial screening with "abdominal pain/discomfort, constipation or diarrhea on an average of 4 days a month in the previous 12 months?" Subsequent items verbatim for Rome II, Manning (≥3 symptoms) and 4 other criteria types Prevalence (%): Manning (10.3), Rome II (3.3), others (2.1–12.1)
Chey [54]	US (national), random, geographically stratified, telephone survey; 1350 contacted, 1010 (75%) respondents (100% female) Two pain and duration/frequency items: (1) "In the past 12 months. . .continuous or repeated discomfort or pain in your lower abdomen or bowels for. . .at least 3 months?" (2) "Not counting menstrual pain, have you ever experienced recurring pain or discomfort in your lower abdomen or bowels of 3 months or longer?" Prevalence (%): Rome II (item 1, 5.4; item 2, 8.3)
Thompson [75]	Canada (national), random, geographically stratified, telephone survey; 10,613 contacted, 1149 (11%) respondents (51% female) Pain and duration/frequency: "In the last 3 months did you often (at least 3 weeks [at least once a week]) have abdominal discomfort or pain?" Prevalence (%): Rome II (12.1), Rome I (13.5)
Saito [76]	US (Olmsted County), population-based, self-report (mailed), questionnaire; 892 contacted, 643 (72%) respondents (52% female) Same questions for Rome II, Rome I, "Rome 1989" (31) and "Rome 1990" (32) criteria Pain and duration/frequency: "In the past 3 months have you had continuous or recurrent discomfort or pain in your lower abdomen?" Prevalence (%): Rome II (4.7), Rome I (6.8), "Rome 1989" (25.7), "Rome 1990" (4.8) Age- and gender-adjusted prevalence (%): Rome II (5.1), Rome I (6.8), "Rome 1989" (27.6), "Rome 1990" (5.1)

not attributable to IBS, did not contribute to the accuracy of the score. Furthermore, other investigators failed to confirm the scoring system usefulness [58]. In a recent logistic regression analysis, age over 50 years at symptom onset and a history of blood on the toilet paper were independently associated with lower GI disease, and female sex (also termed an alarm feature) was related to IBS. A model incorporating three Manning symptoms and alarm features yielded correct diagnoses of IBS and

organic lower GI illness in 96% and 52% of cases, respectively [59], corroborating the diagnostic value of the combination of Rome I criteria in the absence of alarm features [53].

Irritable bowel syndrome severity

Although the Rome II criteria for functional constipation and functional diarrhea require certain proportions of bowel movements to be abnormal, there are no severity criteria for IBS. Abdominal pain severity is an independent predictor of quality of life [60]. Abdominal pain is also the most important factor associated with health care use [61], and diverse health care costs were increased 35%, 52%, and 59% in sigmoidoscopy patients with mild, moderate, and severe IBS-related abdominal pain/discomfort compared with non-IBS subjects [62]. The Rome II criteria identify individuals with a wide range of severity of abdominal pain and bowel dysfunction. A symptom severity threshold for the Rome criteria would require a simple statement that takes into account issues related to definitions and symptom meanings. A recently developed IBS-specific symptom questionnaire could be useful in characterizing symptom severity at entry and during clinical trials, as it is short, valid, and responsive to change [63].

Use of symptom criteria in practice

Most family practitioners who have been questioned have not heard of the Manning or Rome criteria [64–66] or recognized the Rome II symptoms as typical of IBS [66], and they tended to diagnose IBS with little testing [67,68]. Sixty-three percent of 100 Dutch family physicians thought that recurrent abdominal pain for more than 3 months was the crucial diagnostic symptom [64]. Of the 142 patients they diagnosed with IBS, 62% had at least two Manning symptoms, but only 18% fulfilled the Rome II criteria. Additional surveys revealed that only 37% of assessed British family practitioners usually diagnosed IBS confidently on the initial visit, and a small group of California general practitioners rated IBS as only fourth in diagnostic confidence out of five chronic, painful syndromes [66].

In contrast, 81% and 83% of 200 British gastroenterologists had heard of the Manning and Rome symptoms, respectively, but they used these criteria in evaluating only 37% and 40% of patients [65]. Thus, uncertainty remains about how IBS is diagnosed in primary care and specialist practice. Boyce et al suggested that the Rome II criteria might be unnecessarily restrictive for use in practice but are suited for research [69]; the Manning symptoms accompanied by chronic abdominal pain without alarm features might be more suitable for practice. Gastroenterologists should educate family practitioners on the typical symptoms and diagnosis of IBS, but strict adherence to a particular set of criteria is not supported by evidence. Because treatment is symptom-based (and often less than optimal), a pragmatist might feel that

clear separation of the functional bowel disorders in practice is also unnecessary. On the other hand, the many physicians who do seek criteria symptoms while taking a history have found them important in managing patients.

To which patients does criteria-related irritable bowel syndrome research apply?

Primary care physicians manage most patients with IBS, but most research has been conducted on patients referred to specialists. In a Minnesota community, for example, only 5% of IBS diagnoses were made by gastroenterologists [69]. Research on referred patients or those with treatment-resistant symptoms may not apply to primary care patients.

Also, patients enrolled in trials do not necessarily resemble those seen in primary care or referral practice, as reflected by three groups of patients enrolled in a mock trial, all of whom met Rome I criteria, had at least moderate symptom severity and lacked alarm features [70]. British primary care patients tended to be anxious, smokers, and daily alcohol drinkers who had sought care recently for IBS and had tried antispasmodic drugs. California subjects recruited through newspaper advertisements were the oldest, most highly educated, most often depressed, and were least likely to have recently sought care for IBS. A California gastroenterologist's patients tended to be anxious and had nearly all sought care for symptoms, which were the most severe and most likely included all three of the pain-related Manning symptoms. Multivariate analysis showed that Dutch internal medicine patients were more likely than primary care patients to report severe abdominal pain and have more additional complaints and more interference with daily activities; they were less likely to attribute their symptoms to stress [71]. Ethnicity also could influence the features of patients recruited for studies, as US Hispanics were less likely than non-Hispanic whites to have seen a physician for IBS symptoms, had a poorer perception of their general health, and had more likely used folk remedies and herbal teas [72]. Use of translated questionnaires in cross-cultural practice or research introduces potential miscommunication of meaning, and Sperber has detailed a method of validity testing of such instruments [73].

Summary

The symptom-based taxonomy of IBS and other functional bowel disorders is based on defined individual symptoms and the co-occurrence of certain symptoms in individuals. Wording of survey questions to accurately reflect the symptoms can be difficult in English, but accomplishing it for non-English-speakers, especially residents of non-Western societies, is an even greater challenge that needs more attention. The potential for misdiagnosis

and inappropriate management, including unnecessary surgery [74], underscores the need for wider knowledge of typical IBS symptoms by physicians and the collaboration of primary and specialist physicians in patient care. Even though the evolving symptom classification is as evidence-based as its designers can make it, some arbitrariness is inevitable. Population prevalence rates vary widely, depending on diagnostic criteria and other factors, and further work is needed to determine which individuals detected in surveys consider themselves distressed enough to want medical care and why the remaining people do not feel this need. Clearly, more primary care patients should be studied. Physicians should assess clinical trials critically regarding patient recruitment methods and patient features that could influence whether the results are applicable to their patients. The instability of bowel habit subtypes suggests that relatively few patients should expect relief by taking the same motility-active drug regularly for a long time. Long-term, natural history studies of symptoms and health care use are needed.

Discoveries of subtle morphologic pathology and disordered physiology are elucidating IBS pathophysiology further, which some experts believe will lead to a more objective, laboratory-based (organic) diagnosis and more effective therapy. The benefit patients will obtain from supplementing a traditional symptom-based, biopsychosocial approach with such findings remains to be determined.

The symptom criteria have had important roles in epidemiological studies and characterizing subjects for clinical trials. Many practitioners, however, do not know the typical symptoms or use the criteria, and investigating how physicians diagnose IBS has received scanty attention. It is unknown how many physicians diagnose IBS by exclusion only after extensively testing patients with typical symptoms and no alarm features, but determining this could have important economic and safety implications. There has been little careful validation of the symptom criteria, especially with primary care patients, and no particular criteria are clearly superior for clinical practice, although the Manning and Rome I criteria have been most evaluated and are less restrictive than the Rome II criteria.

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Irritable Bowel Syndrome: Epidemiology, Natural History, Health Care Seeking and Emerging Risk Factors

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Irritable bowel syndrome (IBS) is a clinical syndrome in which chronic abdominal discomfort or pain occur with disturbed bowel habit not explained by an established organic or biochemical abnormality [1]. The definition of IBS has evolved from a diagnosis of exclusion to making a confident positive diagnosis based on standard criteria [2–4]. IBS is one of the most common occurrences in outpatient medicine and the most frequent reason for consultation with a gastroenterologist [5]. Because a limited proportion of subjects suffering from IBS seeks medical attention for this condition [5], knowledge of IBS epidemiology depends on research in the general population to estimate the disease burden and to plan management and public health interventions.

This article provides a critical overview of the status of knowledge on IBS epidemiology, natural history, health care seeking, and emerging risk factors. The authors critically selected relevant papers from a systematic review of the electronic literature databases (PubMed, Embase) performed using the search terms irritable bowel, epidemiology, prevalence, incidence, natural history, risk factor, care seeking, and consulting. The emerging risk factors are discussed without focusing on pathogenic mechanisms, which are covered elsewhere in this issue.

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Epidemiology

IBS epidemiology varies considerably according to the definition used. The earlier Manning criteria are more general and less restrictive than the more recent Rome 1 and Rome 2 criteria [2–4]. Thus, studies using the Manning criteria to define cases of IBS tend to report higher prevalence rates than studies using the Rome criteria. IBS prevalence, gender distribution, and clinical spectrum seem to vary between western countries and Asia, and pertinent data are reported separately (Fig. 1).

Prevalence in western countries

In Table 1, data from major IBS epidemiological studies in western countries are summarized. Prevalence estimates across studies are quite wide, ranging between 3% and 25%, but most studies suggest the prevalence is around 10% depending on the definition applied.

In some studies there is a predominance of female gender with a female:male ratio reaching 3:1 [6,7]. The ratio is lower in population-based data, especially in the studies conducted in the Olmsted County population using either Manning or Rome criteria [8,9]. Although in earlier studies IBS seemed more common in younger age groups [6,10], other surveys have not confirmed this trend [11].

There is minimal information on the prevalence of IBS subtypes based on predominant bowel habit. A pooled analysis of data from different surveys on random samples in the Olmsted County showed an age-adjusted prevalence of 5.5% for diarrhea-predominant IBS and 5.2% for both constipation-predominant IBS and IBS with alternating bowel habit [10].

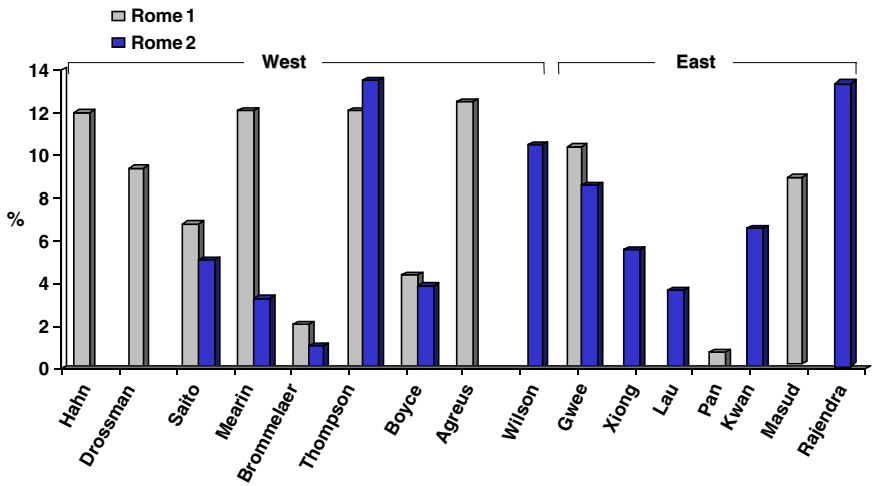

Fig. 1. Prevalence of IBS in western countries (West) and Asia (East) according to Rome 1 AND Rome 2 criteria.

Table 1
Irritable bowel syndrome prevalence: studies in western countries using the manning and/or the Rome criteria

Author	Setting	N	Survey method	IBS definition	Prevalence (%)
Talley [8]	Olmsted County, Minnesota	835	Mailed questionnaire	Manning	12.8
Hahn [7]	NHIS	42,392	Face-to-face interview	Manning	3
				Rome 1	12
Drossman [6]	United States, householder	5430	Phone interview	Rome 1	9.4
Saito [9]	Olmsted County, Minnesota	643	Mailed questionnaire	Manning	15.7
				Rome 1	6.8
				Rome 2	5.1
Mearin [80]	Spain, population random sample	2000	Face-to-face interview	Manning	10.3
				Rome 1	12.1
				Rome 2	3.3
Brommelaer [66]	France, population quota sample	8221	Phone interview	Manning	12
				Rome 1	2.1
				Rome 2	1.1
Thompson [67]	Canada, general practice	3111	Questionnaire	Rome 1	12.1
				Rome 2	13.5
Boyce [68]	Australia, urban population	4500	Mailed questionnaire	Manning	13.6
				Rome 1	4.4
				Rome 2	3.9
Jones [69]	England, general population	1620	Mailed questionnaire	Manning	22
Agreus [21]	Sweden, general population	1290	Mailed questionnaire	Rome 1	12.5
Wilson [70]	United Kingdom general practice enrollees	8386	Mailed questionnaire	Rome 2	10.5

This study showed that a proportion of subjects had neither predominant constipation nor diarrhea, but still met the Manning criteria [10]. Factor analyses of symptom groupings among different populations show the distinction into predominant bowel habit can be difficult. Upper and lower gastrointestinal (GI) symptoms seem to be grouped distinctly across populations, but the clustering of a definite bowel habit with IBS symptoms is less consistent [12].

Prevalence in Asia

Table 2 summarizes data for prevalence studies in Asian populations. The prevalence rates in the Asian studies have been generally lower than in

Table 2
Irritable bowel syndrome prevalence: studies in Asia

Author	Setting	N	Survey method	IBS definition	Prevalence (%)
Gwee [13]	Singapore	2276	Face-to-face interviews	Manning	11
				Rome 1	10.4
				Rome 2	8.6
Xiong [14]	South China	4178	Face-to-face interviews	Manning	11.5
				Rome 2	5.6
Lau [18]	Hong Kong	1298	Face-to-face interviews	Rome 2	3.7
Pan [71]	China	2486	Questionnaire	Manning	7.3
				Rome 1	0.8
Ho [72]	Singapore	696	Face-to-face interviews	Manning	2.6
Kwan [15]	Hong Kong	1797	Phone interviews	Rome 2	6.6
Danivat [73]	Thailand	1077	Questionnaire	Manning	4.4
Masud [17]	Bangladesh	2426	Face-to-face interviews	Rome 1	8.5
Rajendra [16]	Malaysia	949	Face-to-face interviews	Rome 2	14

western studies, whichever criteria are applied, and there is more between-study heterogeneity in the estimates, possibly explained by the different nature of the population surveys (rural versus urban). Indeed, two studies on urban populations in Malaysia and China [13,14] report rates similar to those observed in the west. The female:male ratio across Asian studies most commonly is around 1.5 [13–17]. There is some controversy on which is the most common IBS subgroup. One study in southern China found the diarrhea-predominant group was more common (74%) [14], while in a Singapore study 51% of patients had constipation, and only 12% had diarrhea as their predominant bowel habit [13]. In virtually all studies, IBS was more common in younger age groups. There seem to be differences between east and west in disease epidemiology and clinical features. Heterogeneity in study methodology, sampling frames and, in some instances, low response rates [18], however, make data interpretation difficult.

Incidence

The available data on IBS incidence (Table 3) are based on survey research studies in which questionnaires repeatedly were sent to a population random sample. IBS onset rate measured from two questionnaires mailed 12 to 20 months apart was 9% in a United States study [19]. This can be deemed representative of the rate of onset IBS of episodes, however, rather than the true incidence. Another study in the same geographical setting, but using patient charts to determine new physician-based IBS diagnoses provided an overall gender-adjusted incidence rate of clinically diagnosed IBS of 196 cases per 100,000 person-years (95% confidence interval [CI], 153 to 232) [20]. This latter study provides an incidence estimate that is likely to be much lower than the actual one, as it was based on subjects presenting for consultation from the general population who had received a clinical

Table 3
Studies on the incidence of irritable bowel syndrome

Author	Setting	N	Survey method	IBS definition	Incidence
Talley [19]	US general population random sample	582	Mailed questionnaires	Manning and Rome 1 criteria	9%
Locke [20]	Physician-based diagnosis in the population	416	Review of all physician-based IBS diagnoses	Physician-based and reviewed by investigators	2/1000 person years
Agreus [21]	General population random sample	1290	Mailed questionnaires	Rome 1	2/1000 over 3 months
Rodriguez [22]	British database of general practice enrollees	844,690	Physician-based diagnosis	Individual physician-based	2.6/1000 person years

diagnosis of IBS. These figures, however, are similar to those obtained in European studies. A Swedish population-based survey using repeated questionnaire mailings showed incidence to be two cases per 1000 population over a 3-month interval [21]. A British database study estimated the yearly IBS incidence at 260 cases per 100,000 people [22]. No data are available on IBS incidence in Asian countries.

Natural history

Symptom fluctuation, overlap, and probability of organic disease

IBS is characterized by fluctuation of symptoms, sometimes between the different bowel subtypes, and by periods of symptom remission [23]. These characteristics make it difficult to plan long-term therapeutic studies. Over a 1-year period, 30% of subjects reported IBS symptom resolution [19]. This disappearance rate does not seem to result in longer-term complete resolution, however, as only 5% of patients reporting IBS were found to be symptom-free at 5 years of follow-up [24]. Using the Manning criteria, the prevalence in the general population of IBS after 1 year has been shown to change only from 17% to 18%, and from 7 to 8.0% using the Rome criteria [19]. This suggests that despite patients experiencing remission or having a change in their symptom pattern, the proportion of subjects fulfilling criteria for IBS in the population remains relatively stable. IBS symptom resolution, however, does not necessarily mean symptom-free status. Up to 45% of patients may transition to symptoms consistent with another functional GI disorder, such as functional dyspepsia or gastroesophageal reflux [23] (Fig. 2). Despite this overlap with other functional bowel disorders, the diagnosis of IBS appears to be relatively durable. A retrospective population-based cohort of 149 patients who received an IBS diagnosis (only 5% in tertiary care setting) showed that 0.7% of patients

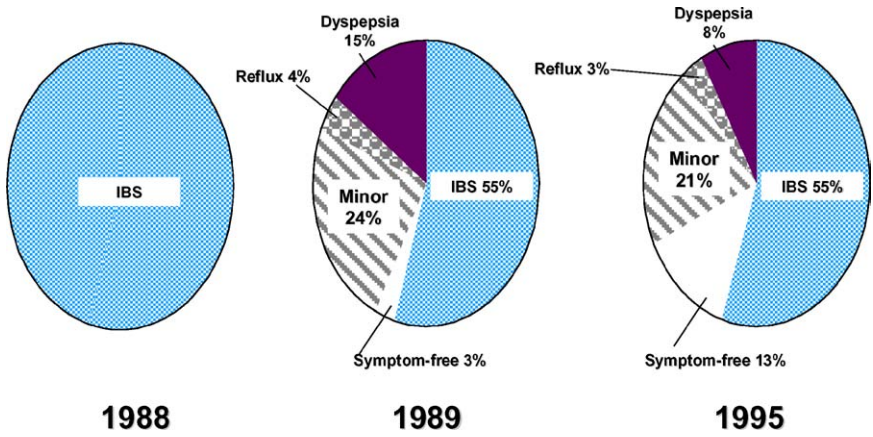

Fig. 2. Irritable bowel syndrome (IBS) and fluctuation of symptoms. At least 45% of IBS patients will report change in symptom pattern over time, fulfilling criteria for other functional gastrointestinal disorders. The overall proportion of patients affected by IBS over time in the population seems to remain stable, however. (*Adapted from* Agreus L, Svardsudd K, Talley NJ, et al. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. Am J Gastroenterol 2001;96(10):2905–14; with permission).

developed an organic disease over a 3-year postdiagnosis period [25]. According to a large United Kingdom database study, 1% of patients receiving an IBS diagnosis from their primary care physician were later (within 1 year) found to have a colorectal tumor, an incidence similar to that in the general population; 0.6% subsequently were diagnosed with inflammatory bowel disease [22]. When diagnostic criteria for IBS are applied, and routine diagnostic tests are performed, less than 1% of patients ultimately will be found to have colon cancer, according to a systematic review [26]. This estimate seems more robust than that from earlier studies on IBS, conducted in a clinic-based setting and suggesting a rate of ultimate organic disease diagnosis between 0 and 6.5% [27–30].

Surgery and irritable bowel syndrome

Because of symptom overlap with other disorders or because of improper diagnosis, patients with IBS often undergo unnecessary surgery. Hasler and Schoenfeld pooled data from two population-based studies, and found patients with IBS compared with controls had an increased prevalence of cholecystectomy (4.6% in IBS versus 2.4% in controls, odds ratio [OR], 1.9; 95% CI, 1.2 to 3.2) and of hysterectomy (18% in IBS versus 12% in controls OR, 1.6; 95% CI, 1.1 to 2.2) [31]. A recent multivariate analysis conducted on a random sample from a large health care provider database shows IBS patients report more frequently than controls cholecystectomy (12% versus 4%), appendectomy (21% versus 12%), hysterectomy (33% versus 17%), and back (4% versus 3%) surgeries [32]. Socio–demographic factors (such

as a higher education and white race), clinical and psychiatry history features (abuse, depression, or fibromyalgia), and comorbidities (diabetes or hypertension) were associated with each type of surgeries. Although some of these associations with surgery can be explained in terms of more frequent access to health care, none of these variables were associated with symptom resolution after surgery.

Health care seeking

As up to approximately 50% of individuals suffering from IBS will seek health care for their GI symptoms according to estimates in western [33] and Asian populations [13], research has been performed to identify the factors associated with health care seeking.

Most studies investigating predictive factors of consulting a physician for IBS have been population-based case–control studies (Table 4). Older age

Table 4
Studies on predictors of health care seeking in irritable bowel syndrome

Author	N, sample features	Design	Consulting rate (%)	Predictors
Drossman [35]	72 IBS consulters, 82 IBS non-consulters, 84 normal controls	Case-control	N/A	Pain, diarrhea, abnormal personality patterns, coping capability, disruption of daily life by illness
Smith [42]	97 IBS consulters	Case series	N/A	Anxiety, depression, stress, lack of social support, somatization, and abnormal illness behavior
Heaton [36]	1896 population random sample	Postal survey	50	Number of symptoms, abdominal pain
Whitehead [41]	10 IBS consulters, 16 IBS non-consulters 46 symptom-free controls	Case-control	N/A	Psychologic symptoms
Talley [37]	730, population random sample	Postal survey	73	Increasing pain severity, duration of pain, gender, psychological morbidity; abuse history not a predictor
Koloski [38]	481, population random sample	Postal survey	42	Psychological distress, anxiety about abdominal pain
Welch [74]	26 IBS consulters, 41 IBS non-consulters 50 controls	Case-control	N/A	Anxiety, depression, obsessive compulsion, and interpersonal sensitivity were not predictors.

consistently is associated with consulting a physician for IBS symptoms [10]. The female to male ratio of IBS patients in the clinic setting is about 3:1, while in the general population it is between 1:1 and 2:1 [34], suggesting gender is a predictor of consulting behavior. Specific symptoms also may drive consultation, with abdominal pain being the most constantly associated along with symptom duration and, specifically, duration of pain [35–38]. Psychological distress, coping strategies, and somatization also appear to be related to health care seeking across different studies, while a history of abuse does not seem to be a significant factor [37]. When analyzing studies on health care seeking predictors, sampling and measurement biases must be taken into account. In fact, the evidence available is based on different measures for psychosocial factors, and the predictors identified failed to explain most health care seeking.

Emerging risk factors

IBS is a multifactorial condition in which GI motor and sensory dysfunction and psychological traits may contribute, in combination with a series of environmental factors such as acute GI infections and food intolerance. There also may be a background genetic predisposition [39]. Research on classical risk factors such as smoking and alcohol consumption has shown no association [10,24]. Several difficulties are encountered in performing and interpreting studies of risk factors in IBS. There is the potential for recall bias in case–control research (for example, subjects suffering from a condition may be more prone to report exposure to certain risk factors, when specifically asked), and the sampling frame used is crucial (clinic-based may provide more biased information than population-based studies). Also of major relevance are the statistical power attained (for example, large sample sizes are needed to demonstrate associations of relatively low strength that may have important conceptual and practical implications, such as genetic associations) and the use of valid and reliable instruments to identify and measure the disease and the potential risk factors.

Psychological factors

Symptoms of anxiety, depression, and somatization disorder commonly are found in IBS. The overlap between IBS and psychiatric disorders has been found in between 54% and 94% of cases [40]. These disorders, however, are likely to be highly prevalent in the general population. Psychiatric symptoms have been found to be a predictor of health care seeking [35,41,42], at least partially explaining the increased anxiety and neuroticism found in IBS patients as opposed to controls [43,44]. Conceivably, studies on referral population will overestimate the role of psychological factors in IBS. A recent birth cohort study from Dunedin,

New Zealand, reported that IBS was neither associated with an overall diagnosis of psychiatric illness, nor with a history of anxiety, depression, or substance dependence [45].

Socioeconomic background

A poorer socioeconomic background during childhood has been associated with worse health care outcomes in adult life [46,47]. In IBS, a patient-based study found a significant association between childhood higher affluence and positivity to the Manning criteria [48]. These apparently paradoxical data have been confirmed in a large birth cohort, where declining socioeconomic status during childhood was linearly associated with lower trends of IBS prevalence in adulthood (at age 26) according to both Manning and Rome I criteria [49]. These results are in contrast with earlier data on the United States householder survey, reporting higher IBS prevalence in lower income groups [6].

One potential explanation for these findings is that higher socioeconomic status is linked to better access to health care or to a greater tendency to seek a physician's advice and diagnosis. Moreover, in higher social classes, behaviors leading to internalization of stress also may be endorsed, and this component (rather than stress itself) may be associated with functional GI disorders [44]. Alternatively, one might hypothesize that certain infections acquired in childhood may protect against IBS in adulthood, or that encouragement in the family environment toward certain dietary choices or food avoidances (more common in higher income populations) [50] might be relevant.

Postinfectious irritable bowel syndrome

Some patients with IBS have the onset of their symptoms after an episode of acute gastroenteritis. Population-based studies provide a less biased estimate of the true incidence of IBS after infection, and Fig. 3 summarizes the incidence of IBS after infectious gastroenteritis found in different studies. A United Kingdom population-based case–control study found subjects with documented bacterial enteritis (*Campylobacter* or *Salmonella*) had a relative risk of 11 of receiving a diagnosis of IBS over 1 year compared with control subjects with no previous infection [51]. The duration of the initial episode has been found to be a strong predictor of symptom persistence [52], and psychological factors also have been shown to be associated with the development of IBS [53]. Molecular variables related to the host–pathogen interaction and a genetic predisposition could contribute to the outcome [52].

It is unclear whether these patients have a different response to therapy than those without preceding gastroenteritis. The rationale for using antiinflammatory agents after the infection has disappeared has been tested

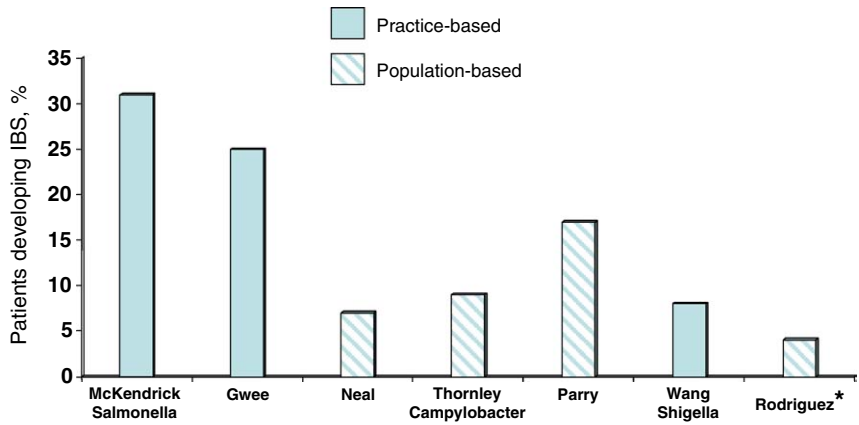

Fig. 3. Incidence of irritable bowel syndrome after an acute gastroenteritis according to different studies [*51,53,75–79]. As expected, incidence is higher in practice-based than in population-based studies. One study is from China and shows an incidence similar to the other European studies [79]. Data are proportion of subjects (%) except in one study [51], where incidence/100 person-years is reported. When studies are based on single bacterial infection, the agent is reported below the study first author.

in one controlled trial of high-dose prednisone in postinfectious IBS patients, which showed no benefit [54]. Thus, the clinical usefulness of defining postinfectious IBS patients as a separate subset remains unclear.

Food challenges

Patients with IBS often report specific foods aggravate their symptoms [55]. Only in a small proportion of subjects attributing their symptoms to food allergy will the presence of a specific allergic reaction ultimately be established. A large outpatient study in Italy found the concordance between reported and actual food allergies was poor across all different food antigen groups, and no association was found between positive allergy testing and IBS subtypes in this study [56].

A North American population-based study found that about 25% of the general population reports food sensitivities, and that there was an independent association between IBS and reported food sensitivities (OR, 2.3, 95% CI, 1.41 to 3.93) [57]. As expected, only a small proportion of patients in this study also reported symptoms consistent with a true allergy, but in this subset, the association with IBS was even stronger [57]. Others have suggested that patients with IBS tend to report problems with food in general, leading to the speculation that IBS itself may be cause, rather than consequence, of food sensitivities [57].

A recent well-conducted randomized trial in the United Kingdom outpatient setting compared the effects of avoidance versus sham diet in IBS patients with positive IgG antibodies to food [58]. The true avoidance

diet led to 20% lower symptom severity at 12 weeks in the subgroup of patients showing full adherence to the assigned diet. On the secondary individual symptom endpoints, however, only noncolonic symptoms were improved in this subgroup [58]. The size and strength of these effects suggest food sensitivities may not be a major risk factor in IBS.

Familial aggregation and genetic predisposition

Common environmental factors in the family and genetics could all play a role in IBS. A population-based, case–control study showed subjects reporting a family member with abdominal pain or bowel symptoms had a twofold odds of reporting IBS symptoms (OR, 2.3, 95% CI, 1.3 to 3.9) [59]. In another population-based study, a symptom questionnaire was sent to first-degree relatives and to spouses' relatives (used as control group) of clinic patients and cases identified from community-wide medical records with IBS. IBS was significantly more prevalent in patients' relatives than in their spouses' relatives (OR, 2.7, 95% CI, 1.2 to 6.3) [60]. These data support the hypothesis that there is a familial component in IBS. Twin studies have been conducted to test for the hypothesis that this contribution might be genetic. An Australian twin registry study showed 57% of the variance in reporting functional GI symptoms in these individuals was attributable to genetic factors, with 43% of the variance seeming to be explained by the individual's unique environment [61]. Concordance in symptom reporting was higher in monozygotic (17%) than in dizygotic twins (8%) in a large United States twin pair study, confirming the role of a genetic background in IBS [62]. In addition to the genetic contribution, having a mother or a father with IBS was a stronger predictor, suggesting family learning remains a major contributing factor [62].

If there is a genetic contribution in IBS, this would be more likely polygenic than monogenic. Relevant genes for IBS have been sought based on pathophysiological models of altered gut motility and sensation. In a relatively small ($N = 54$) study from Turkey, 88% of patients with diarrhea-predominant IBS were found to be carrier of the long/short serotonin transporter promoter (SERT-P) genotype [63]. A larger study explored the distribution of SERT and alpha adrenergic receptor polymorphisms in a North American patient and control population; no significant differences in the polymorphism distributions were observed between IBS patients and controls [64]. A combination of polymorphic SERT-P (SLC6A4) and alpha2C Del 322-325, however, was associated with high somatic symptoms scores, suggesting these polymorphisms might predispose to somatization or other psychological traits associated with IBS [64]. The search for other genes and polymorphism associations, including the polymorphisms in the gene encoding the GNβ3 G-protein (which has been associated with functional dyspepsia [65]), is underway, and this topic is dealt with comprehensively elsewhere in this issue.

Summary

IBS is a common condition, affecting approximately 3% to 15% of the general population based on various diagnostic criteria. There seem to be differences in disease epidemiology between the eastern and the western world. As data from larger Asian epidemiological studies begin to surface, however, such differences appear to be less marked. The proportion of IBS patients who consult a physician for their symptoms is around 50%. Psychological factors and the presence and duration of abdominal pain are all significant predictors for health care seeking. The natural history of IBS is characterized by frequent fluctuation of symptoms and by an overlap with other functional GI disorders, some of which share a number of risk factors for IBS. Unnecessary abdominal surgery is performed in a high proportion of IBS sufferers. Along with the established role for psychosocial conditions in IBS, other risk factors are emerging. Evidence for postinfectious IBS is mounting, but the clinical usefulness of characterizing such patients remains unclear. Food sensitivities are frequently present in IBS, but more well-conducted trials of avoidance diets and desensitization are needed. Finally, genetic markers in IBS are an increasing focus of attention, but the amount of phenotypic variance explained by genetic variability remains to be established.

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Diagnosis of Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is characterized by the presence of chronic or intermittent abdominal pain in association with changes in stool frequency or consistency. As there is no single biological marker that can identify patients with this common disorder, IBS traditionally has been viewed as a diagnosis of exclusion. Converging lines of evidence, however, suggest that most patients with IBS can be diagnosed confidently by using symptom-based criteria, excluding red flags or alarm features, and the judicious, individualized application of diagnostic tests. This article critically evaluates the evidence that supports this contention.

Symptom-based criteria for irritable bowel syndrome

In an attempt to simplify and standardize the diagnosis of IBS, multiple symptom-based criteria (Table 1) have been developed, including the Manning, Kruis, Rome (1988), Rome (1990), Rome I, and Rome II criteria [1–4].

Among the commonly used symptom-based criteria, the Manning criteria have been the most extensively evaluated. The Manning criteria first were published in 1976 and consisted of six symptoms that discriminated between patients diagnosed with IBS and organic gastrointestinal (GI) disease [1].

The opinions and assertions contained herein are the sole views of the authors and should not be construed as official or as representing the views of the US Navy, Department of Defense, or Department of Veteran Affairs.

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Table 1
Symptom-based criteria for the diagnosis of irritable bowel syndrome

Manning criteria	Rome criteria	Rome II criteria
Abdominal pain relieved by defecation	At least 12 weeks of continuous or recurrent symptoms of the following:	At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of the three features:
Looser stools with the onset of pain	Abdominal pain or discomfort: (1) relieved with defecation, or (2) associated with a change in frequency of stool, or (3) associated with a change in consistency of stool	Relieved with defecation and/or
More frequent stools with the onset of pain	Two or more of the following, at least on one fourth of occasions or days: (1) altered stool frequency, or (2) altered stool form, or (3) altered stool passage, or (4) passage of mucous, or (5) bloating or feeling of abdominal distention	Onset associated with a change in frequency of stool and/or
Abdominal distension		Onset associated with a change in form (appearance) of stool
Passage of mucous in stools		
Sensation of incomplete evacuation		

The Manning criteria represent the only diagnostic criteria for IBS that have been validated in clinical studies [5–7]. Although the Manning criteria represented a major advance in the struggle to standardize the diagnosis of IBS, they were far from perfect, with a positive predictive value of only 65% to 75% [1].

In an attempt to build upon the strengths, while limiting the weaknesses of the earlier diagnostic criteria, the Rome criteria were developed by the Working Committee for the XIII International Congress of Gastroenterology in 1988. There have been a number of versions of the Rome criteria that have been developed and refined through expert consensus and careful review of the available evidence. The most recent version, Rome II, was published in 1999, and the Rome III consensus is in development. The Rome criteria

have not been validated carefully, although several comparative studies between the different diagnostic criteria are available [8–11].

The primary reason that the Rome criteria were developed was to provide a uniform framework for selecting patients with functional GI disorders, like IBS, for clinical research. In recent years, however, the extension of the Rome criteria to routine clinical practice has been encouraged [12,13]. In an important study, Vanner et al performed retrospective and prospective analyses of patients diagnosed with IBS by the Rome I criteria over a several-year period [14]. The investigators demonstrated that the absence of alarm features in patients who fulfilled the Rome criteria was associated with a durable diagnosis of IBS. In the retrospective arm of this trial, the sensitivity of the Rome criteria, combined with the absence of alarm features, was 65%. The specificity was 100%, and the positive predictive value was 100%, with a negative predictive value of 76%. In the prospective arm of the trial, the positive predictive value of the Rome criteria without alarm features was 98%.

The Rome II criteria for IBS require at least 12 weeks (which need not be consecutive), in the preceding 12 months, of abdominal discomfort or pain that is accompanied by at least two of the following three symptoms. The abdominal discomfort or pain is relieved with defecation, associated with a change in the frequency of defecation, or associated with a change in the form or appearance of the stool [3]. The Rome II criteria have the advantage of being easier to recall and use than the older Manning or Rome I criteria. There is evidence, however, to suggest that the Rome II criteria may be more restrictive than the Rome I criteria, so that some patients diagnosed with IBS according to the Rome I criteria do not fulfill the Rome II criteria. A recent study using telephone interview data from a large, community-based sample of American women assessed the sensitivity of the Rome I and Rome II criteria [15]. When the criteria were applied to over 1000 women diagnosed with IBS by their physician, Rome II was significantly less sensitive than Rome I (49% versus 83%, $P < 0.001$). This difference in sensitivity between the two sets of criteria was largely because of the more restrictive temporal pain requirement of Rome II. There was 47% agreement between Rome I and Rome II (Kappa = 0.296). These findings suggest that Rome II, while useful for identifying actively symptomatic patients for clinical trials, likely underestimates the overall prevalence of IBS. For this reason, Rome II may not be appropriate for epidemiological studies evaluating the lifetime prevalence of IBS. Further, the role of Rome II in routine clinical practice remains poorly defined. Many patients who do not fulfill the Rome II criteria eventually are given a diagnosis of IBS, typically after diagnostic testing to exclude organic GI diseases. To date, the Rome II criteria have not been embraced widely by those in clinical practice. A set of symptom-based criteria specific enough for clinical research but practical enough for clinical practice will be the challenge facing the working group responsible for developing the Rome III criteria for IBS.

General approach to diagnosis

When deciding upon the necessity of a diagnostic test, two issues deserve particular attention. First, one should consider the pretest probability of the disease in question, a determination that is based upon the prevalence of that disease in patients with specific symptoms. If the pretest probability of a particular disease is sufficiently small, then diagnostic testing directed at uncovering that improbable disease is unlikely to be either clinically useful or cost-effective. Second, clinicians should be aware of the performance characteristics (eg, sensitivity, specificity, and positive and negative predictive value) of the diagnostic test under consideration if the pretest probability of a disease is sufficiently high to warrant investigation.

The results of a diagnostic test should shift the clinician's estimate of pretest probability of a disease up or down so that he or she may be reasonably assured that the disease being considered is either present or absent. In the case of IBS, because there are no consistently reproducible anatomic or biologic abnormalities, diagnostic tests are performed to exclude organic diseases that may present with similar symptoms and in so doing, reassure the clinician and the patient that the diagnosis of IBS is correct. Historically, inflammatory bowel disease (IBD), colorectal cancer, systemic hormonal disturbances, enteric infections, and malabsorptive diseases have been of the greatest concern to the clinician faced with a patient with symptoms suggestive of IBS. As one would expect, diagnostic studies designed to identify these conditions are the most commonly performed tests in patients with suspected IBS. Prevalence rates (pretest probability) for these organic GI diseases, based on a recent systematic review of diagnostic testing in patients with suspected IBS, are presented in Table 2 along with prevalence rates of historical non-IBS controls [16]. Although the data are limited, the prevalence of most organic GI diseases does not appear to be significantly different between patients with IBS symptoms and the normal population rates. These observations might be used by some to conclude that no diagnostic testing in patients with IBS is warranted. It is important to realize, however, that these values are subject to regional and demographic variations, are based on studies of variable methodologic quality, and are restricted to patients with IBS symptoms that are not accompanied by alarm features, so such sweeping generalizations may not be appropriate.

Utility of diagnostic testing in irritable bowel syndrome

The Rome committee and many IBS authorities recommend that several tests be considered as part of the diagnostic evaluation of patients with suspected IBS [2,13]. Recent reviews, however, have cast doubt on the need for extensive routine diagnostic testing in patients with suspected IBS [12,16].

Table 2
Pretest probability of organic gastrointestinal disease in patients meeting symptom-based criteria for irritable bowel syndrome

Organic GI disease	IBS patients (pretest probability)	General population (prevalence)
Colitis/IBD	0.51–0.98%	0.3–1.2%
Colorectal cancer	0–0.51%	4–6%
Gastrointestinal infection	0–1.7%	N/A
Thyroid dysfunction	6%	5–9%
Lactose malabsorption	22–26%	25%

From Cash BD, Schoenfeld PS, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol 2002;97:2812–9; with permission.

Routine blood tests

Several reports [17,18] have examined the use of blood tests such as complete blood count (CBC), serum chemistries, and thyroid function tests as part of the diagnostic evaluation of suspected IBS. In the trial by Tolliver et al, CBC and serum chemistries were performed in 196 patients with suspected IBS [17]. In this trial, the results of such tests failed to result in an alternative diagnosis of organic GI disease in any patient. Serum chemistries were abnormal in two patients (1.0%), with both subjects having abnormal liver associated enzymes. Sanders et al evaluated the use of CBC and serum chemistries in patients who fulfilled Rome II criteria for IBS [18]. Through these routine blood tests, they identified 6 out of 300 patients (2.0%) with organic GI diseases. One patient was anemic and later found to have celiac disease, and two patients had abnormal liver associated enzymes that were attributed to excess alcohol intake. Cessation or limitation of alcohol intake resulted in resolution of these laboratory abnormalities, but the effect of this intervention on IBS-like GI symptoms was not reported. Two patients had elevated C-reactive protein levels, and one had an elevated erythrocyte sedimentation rate (ESR). All three patients subsequently were diagnosed with IBD.

Two studies have evaluated the role of measuring thyroid stimulating hormone (TSH) levels as part of the diagnostic evaluation of patients with suspected IBS. Hamm performed TSH in more than 1200 patients fulfilling the Rome I criteria and identified 67 patients (6%), with thyroid function abnormalities [19]. These abnormalities were distributed evenly between hyper- and hypothyroidism. It is unclear whether the thyroid abnormalities identified were responsible for the patients' IBS symptoms, because symptom response was not reported following correction of the thyroid dysfunction. Tolliver identified 1 out of 171 (0.6%) patients with suspected IBS who had an abnormal TSH [17]. The nature of the thyroid dysfunction was not reported, nor was the impact of therapy for the thyroid abnormality upon GI symptoms. These data must be considered carefully, however, because

thyroid function test abnormalities are common in the general population, with an expected prevalence of 5% to 9% [20].

Antibody testing for celiac sprue

Gluten sensitive enteropathy, or celiac disease, has received increased attention over the last several years as a potential source of GI symptoms that could be mistaken for IBS. Recent evidence suggests a higher prevalence of celiac disease in the general population than previously estimated. A large United States study by Fasano et al recently reported a prevalence of celiac disease of 1 out of 133 in the general population [21]. Prevalence rates were even higher for those with GI symptoms (1 out of 56) and in those with a first-degree relative with celiac disease (1 out of 22). The breadth of the celiac disease iceberg also is becoming better understood. There is now general consensus that the classic presentation of celiac disease described by Samuel Gee in 1888 is singularly uncommon [22]. Patients with celiac disease are much more likely to present with vague abdominal symptoms, generalized fatigue, or with anemia discovered during routine health maintenance [23]. It is also likely that, given the most recent prevalence estimates of celiac disease, most patients with the condition remain undiagnosed, even with continued gluten exposure. In a recent survey of 1032 Celiac Disease Foundation members, 77% reported that their presenting symptoms consisted of abdominal pain or bloating; 73% had gas or bloating; 52% had diarrhea; 24% had varying diarrhea or constipation, and 7% presented with constipation. All of these symptoms could, given the appropriate chronicity, be supportive of a diagnosis of IBS [24]. When the Rome II criteria were applied to respondents, 17% fulfilled criteria for IBS; however, 37% reported that they had been labeled as suffering with IBS before being diagnosed with celiac disease. Patients participating in this survey saw an average of three physicians before the diagnosis of celiac disease was made, and the median time from physician visit to definitive diagnosis was 12 months. Further, it recently was suggested that a subset of patients with celiac disease may have negative serological tests (latent celiac disease) or normal histology (potential celiac disease) [25].

Information about the yield of serological screening for celiac disease in patients with suspected IBS recently became available (Table 3). Sanders performed antigliadin antibody (AGA) testing (IgA and IgG) and endomysial antibody (EMA) testing in 300 patients with IBS as defined by the Rome I criteria and in 300 age- and gender-matched asymptomatic controls to examine the prevalence of celiac disease in patients with IBS symptoms [18]. Positive antibody tests were followed by upper endoscopy and distal duodenal biopsies. Sixty-six patients (22%) with suspected IBS had positive antibody tests, and 14 (4.67%) had histologic evidence of celiac disease compared with two (0.67%) non-IBS controls, suggesting that

Table 3
Studies evaluating the prevalence of celiac disease in patients with suspected irritable bowel syndrome

Author	Country	Subjects	IBS criteria	Celiac disease prevalence (%)
Sanders [18]	UK	300	Rome I	4.7
Sanders [27]	UK	123	Rome II	3.3
Shahbazkhani [28]	Iran	105	Rome II	11.4
Locke [31]	US	50	Manning	4

patients diagnosed with IBS had a sevenfold greater prevalence of celiac disease. Although not reported in their original manuscript, these investigators subsequently reported that among the 14 confirmed cases of celiac disease 13 (93%) experienced improvement of their IBS symptoms 3 to 6 months after initiation of a gluten-free diet [26]. In a subsequent study, Sanders performed immunoglobulin assays and antibody testing for antigliadin and EMA in a cross-sectional population of visitors (patients and non-patients) to five primary care practices in the United Kingdom [27]. Using the Rome II diagnostic criteria during interviews, they determined that 10.5% (123 out of 1200) of the study population had symptoms consistent with IBS. The prevalence of newly diagnosed celiac disease in the study population was 1% (12 out of 1200 patients) and the prevalence of the disease among patients fulfilling the Rome II criteria was 3.3% (4 out of 123) ($P < 0.05$, 95% confidence interval [CI], 0.1% to 0.6%). After 6 months of therapy with a gluten-free diet, 11 of 12 IBS patients diagnosed with celiac disease were re-evaluated, and 10 out of 11 reported improvements in their IBS symptoms.

In a study from Iran, a country thought to have a low prevalence of celiac sprue, Shahbazkhani et al measured serum IgA, AGA, and EMA in 105 suspected IBS patients and one asymptomatic sibling [28]. Upper endoscopy with duodenal biopsies was performed in patients with positive serologic tests. Among patients with suspected IBS, 11.4% (12 out of 105) had positive antibody tests and duodenal histology consistent with celiac sprue. No patients in the asymptomatic control group of siblings had positive antibodies. After a gluten-free diet for 6 months, antibody testing, endoscopy with biopsies, and symptoms were reassessed. Although the follow-up data are incomplete, there is an indication that those able to adhere to a gluten-free diet experienced improvements in IBS symptoms, antibody titers, and duodenal histology.

Similar to observations in patients with IBD, IBS and celiac disease may not be mutually exclusive diseases but in fact, may coexist in the same patient [29]. In a recent study from Ireland, 30 of 150 (20%) patients with biopsy-proven celiac sprue fulfilled the Rome criteria for IBS compared with 8 of 162 (5%) controls [30]. Symptoms of IBS were equally likely in celiac patients compliant with a gluten-free diet compared with those who were

noncompliant. Unfortunately, this study did not include histological assessment of the small bowel mucosa in celiac patients, so it is possible that persistent mucosal abnormalities could have been present in patients reporting GI symptoms.

In a small study from the Mayo Clinic, Locke et al did not find a significantly increased prevalence of celiac disease in patients diagnosed with IBS or dyspepsia compared with asymptomatic controls [31]. Among patients diagnosed with IBS, 2 out of 50 (4%, 95% CI, 0.5% to 13.7%) had positive tissue transglutaminase antibodies (TTg) compared with 2 out of 78 in the control group (2.6%, 95% CI, 0.3% to 9%) groups ($p = 0.64$). Similar results were observed with dyspepsia. There was no histological confirmation of the diagnosis of celiac disease, nor was there an assessment of the effects of a gluten-free diet on IBS symptoms among those with a positive antibody test. Perhaps most importantly, this study was underpowered to demonstrate the relatively small absolute differences in the prevalence of celiac sprue between patients with suspected IBS and controls reported by others.

Two cost-effectiveness studies evaluating the role of celiac disease antibody screening in patients with suspected IBS recently were reported [32,33]. Using decision analytic modeling, Mein and Ladabaum concluded that testing patients with suspected IBS with either serum TTg or an antibody panel (TTg, AGA, IGA) was highly cost-effective (cost per quality adjusted life-year gained of $4600 per case for TTg and $8800 per case for the antibody panel) [32]. In a sensitivity analysis, TTg testing remained cost-effective in patients with suspected IBS as long as the prevalence of celiac disease was greater than 1.1%.

Spiegel et al also used decision analysis to explore the cost-effectiveness of testing for celiac disease in patients with suspected diarrhea-predominant IBS (D-IBS) [33]. They biased their model against testing for celiac sprue by assuming low estimates for individual test characteristics, incomplete adherence to a gluten-free diet, and incomplete symptom response in those patients adherent to a gluten-free diet. They assumed a base case celiac disease prevalence of 3.4% in the D-IBS population. Even with the base case assumptions biased against testing for celiac disease, testing of patients with D-IBS was found to be a cost-effective practice. Similar to the model by Mein, this strategy remained cost-effective with a prevalence of celiac disease as low as 1% and became the dominant strategy (money saving) when the prevalence was greater than 8%. As with all decision analytic models, these results should be viewed as hypothesis generating and await confirmation in properly designed clinical trials.

Stool tests

The study by Tolliver also examined the use of fecal occult blood testing (FOBT) in patients with suspected IBS [17]. Fifteen of 183 patients (8.2%)

had a positive FOBT and subsequently underwent full colonoscopic examination. Four of the 15 with positive FOBT, or 2.2% of the original cohort, had structural abnormalities identified during colonoscopy. None of these findings were felt to represent an alternative diagnosis to IBS, nor were these findings felt to provide an explanation for the patients' IBS symptoms. Examination of stool for ova and parasites is another commonly recommended test for patients with suspected IBS. Two trials have evaluated the results of stool O&P examination in this population [17,19]. Hamm found that 1.7% (19 out of 1154) of patients with suspected IBS had evidence of an intestinal pathogen on standard stool O&P examination. Of these 19 subjects, eight (0.69%) were colonized with *Blastocystis hominis*, a relatively common organism of unclear clinical significance [19]. Clinical outcomes following eradication of the identified pathogens were not reported, so proof of causality remains unestablished. Likewise, Tolliver performed stool O&P examinations in 170 patients with suspected IBS and found no subjects with evidence of enteric infection [17].

Hydrogen breath testing

The prevalence of lactose malabsorption (typically diagnosed by abnormal hydrogen breath testing) is estimated to be approximately 25% in western countries and perhaps as high as 75% worldwide [34,35]. Several trials have reported the results of hydrogen breath testing for lactose malabsorption in patients with suspected IBS [17,19,36]. One trial found that 23% (256 out of 1122) of patients with suspected IBS, when administered an oral 25 g lactose dose, demonstrated impaired lactose absorption [19]. Response to a lactose-free diet was not reported, so it impossible to determine how many of these subjects actually had GI symptoms because of lactose malabsorption. In another study, 186 patients with suspected IBS were evaluated with hydrogen breath testing (50 g dose of lactose) [17]. These investigators found a similar prevalence of lactose malabsorption, with 25.8% (48 out of 186) of the cohort having abnormal results. In a subsequent publication, reflecting 3 years of follow-up, these investigators demonstrated that patients diagnosed with lactose malabsorption did not differ with respect to their ongoing GI symptoms when compared with patients without evidence of lactose malabsorption [37]. In contrast to these findings, Bohmer and Tuynman observed significant improvements in IBS symptom scores and reductions in health care use in 75% of lactose-intolerant IBS patients following education and dietary intervention over a period of 5 years [38]. Vesa et al from Finland identified lactose intolerance, by means of the ethanol lactose tolerance test, in 23.7% (101 out of 427) of a healthy cohort [36]. Using the Rome I criteria, 15% of lactose digesters and 15% of lactose maldigesters fulfilled criteria for IBS. Although this trial was not designed to evaluate the role of lactose maldigestion on IBS symptoms, the findings of comparable IBS prevalence

in lactose digesters and maldigesters suggest that lactose maldigestion did not play a significant role in the etiology of IBS symptoms. Thus, the prevalence of lactose intolerance in patients with suspected IBS appears to be 15–25%, a prevalence rate very similar to that observed in the general population. Perhaps more importantly, the clinical impact of identifying lactose intolerance in IBS patients remains unclear.

Breath testing also has been used to identify the presence of small intestinal bacterial overgrowth (SIBO). The potential role of SIBO as an etiology for IBS symptoms has been highlighted by two recent publications [39,40]. Pimentel et al performed lactulose hydrogen breath testing in 202 patients fulfilling the Rome I criteria referred for evaluation of possible SIBO [39]. Seventy-eight percent (157 out of 202) had positive breath test results and were treated with a 10-day course of neomycin. Forty-seven patients (29.9%) were restudied 7 to 10 days after completion of the antibiotics, and a negative breath test was documented in 25 patients (53.2%). Twelve patients (48%) with a negative follow-up breath test no longer met the Rome I criteria when their symptoms were reassessed, while only four patients (18.2%) with a persistently positive breath test failed to meet the Rome I criteria after treatment. Although intriguing, this study has been criticized for several methodological issues including potential patient selection bias (given the referral population), the absence of a control group, short study duration, and incomplete follow-up data.

To address some of these concerns, the same investigators subsequently reported the results of a double-blind randomized placebo-controlled trial evaluating the effects of therapy for SIBO upon IBS symptoms [40]. Seven days after completion of neomycin or placebo for 10 days, patients returned for symptom assessment and lactulose breath testing. IBS patients with a negative follow-up breath test result reported significantly greater improvement in IBS symptoms than patients with a persistently abnormal breath test result. although this study is clearly more persuasive than their original work, methodological questions remain regarding the reliability of a lactulose breath test to identify SIBO and the effectiveness of neomycin to treat SIBO. Despite these limitations, these studies raise some intriguing questions about the potential association between SIBO and IBS symptoms.

Abdominal imaging

Francis et al evaluated the role of abdominal ultrasound to identify serious abdominal or pelvic pathology in 125 patients (100 women, 25 men) with suspected IBS by Rome I criteria [41]. Twenty percent of women and 8% of men had some abnormality identified by abdominal ultrasound examination. Ten percent of women had pelvic abnormalities, most of which were gynecological in origin. The prevalence of hepatobiliary abnormalities was similar in women and men (10% and 8%, respectively).

Importantly, the identification of an anatomic abnormality on ultrasound did not lead to additional therapeutic measures in any patient. Further, in no cases were the authors able to correlate the abnormalities identified on ultrasound to the patients' GI symptoms. These investigators concluded that abdominal ultrasound in patients with the positive diagnosis of IBS by means of symptom-based criteria was not necessary and may actually be counterproductive, because identifying trivial anatomic abnormalities could lead to unnecessary patient concern and additional, more invasive tests or procedures.

Colonic imaging

In a small nested case-control cohort study, Lanng et al performed barium enema and measured colonic transit time with radiopaque markers and plain abdominal films and found no difference in the prevalence of organic disease in patients with suspected IBS and asymptomatic controls [42].

Four studies have evaluated formally the yield of endoscopic investigations in patients with suspected IBS. Hamm [19] examined the yield of flexible sigmoidoscopy and colonoscopy in suspected IBS patients fulfilling Rome I criteria. It is not clear from this report how many subjects underwent each individual examination. Among 306 patients studied, four (1.3%) were given alternative diagnoses (three IBD, one colonic obstruction) that may have been responsible for their GI symptoms.

Tolliver performed a similar analysis in 196 subjects with suspected IBS [17]. Like the study by Hamm, the percentage of the cohort that underwent each examination is unclear. Forty-two colonic structural abnormalities were found in 34 subjects. Of these 42 abnormalities, two (1.0%) patients were found to have organic GI diseases (one IBD, one cancer) that could have been potential causes of IBS symptoms. The remainder of the abnormalities consisted of benign polyps, diverticulosis, hemorrhoids, lipomata, and melanosis coli.

MacIntosh evaluated flexible sigmoidoscopy in patients with suspected IBS and in non-IBS controls [43]. Among the IBS cohort, 89% fulfilled the Manning criteria, and 84% fulfilled the Rome I criteria, while in the control group only 15% fulfilled the Manning criteria, and 5% fulfilled the Rome I criteria. Based upon findings at flexible sigmoidoscopy, no patients with suspected IBS were given alternative diagnoses to explain their GI symptoms. These investigators also evaluated the diagnostic yield of rectal biopsies obtained during sigmoidoscopy. No IBS patients or non-IBS controls had rectal biopsy findings that resulted in an alternative or additional diagnosis of organic GI disease.

Finally, Francis et al performed colonic examination with flexible sigmoidoscopy, barium enema, or colonoscopy in 125 patients who fulfilled the Rome I criteria for IBS [41]. Except for diverticular disease that was

judged to be incidental, no organic GI disorders were identified through the performance of these tests, and no patients were given alternative diagnoses to explain their GI symptoms as a result of these examinations.

Diagnosing irritable bowel syndrome in clinical practice

Conclusions from the preceding data must be determined cautiously. Much of the data regarding the yield of diagnostic tests in IBS patients come from tertiary care centers and clinical trials evaluating the efficacy of drug therapies. Such data may not be generalizable to the patients encountered in the primary or secondary care setting. On a purely pragmatic level, many patients with IBS symptoms have waited for extended periods for subspecialty evaluation and may expect some degree of testing to be performed. Further, medical liability issues also contribute to medical decision-making as it pertains to diagnostic testing. The degree to which patient expectations for testing and physician's insecurity about a purely symptom-based diagnosis drives the performance of diagnostic tests remains poorly defined but is undoubtedly substantial.

The American College of Gastroenterology Functional Gastrointestinal Disorders Task Force recently published a clinical practice guideline on the management of IBS in North America [12]. Based upon results from a series of systematic reviews and expert opinion, the task force concluded that the routine performance of diagnostic tests in patients with suspected IBS without alarm features is not supported by the available literature. That is not to say that diagnostic testing never uncovers abnormal results in patients who fulfill symptom-based criteria for IBS. In fact, abnormalities are infrequently identified, but the likelihood of finding such abnormalities is not different in patients with suspected IBS when compared with non-IBS controls. The one possible exception to this statement relates to celiac disease, which may be more prevalent in patients with suspected IBS than in non-IBS controls. As has already been discussed, testing for celiac sprue may be a cost-effective strategy, especially in selected populations (patients of Northern European ancestry, concomitant diabetes mellitus or osteoporosis, or known family history of celiac disease).

The presence of alarm features is felt to identify a subgroup of patients with a greater pretest probability of organic disease. As such, it is entirely appropriate to pursue a more aggressive diagnostic evaluation in these patients. Generally accepted alarm features include new onset of symptoms in patients older than age 50; unexplained weight loss; GI bleeding; progressive or unrelenting pain; nocturnal or large-volume diarrhea; and a family history of colon cancer, IBD, or celiac sprue. Hammer et al recently reported the results of a retrospective review of the predictors of organic GI disease in patients with suspected IBS [44]. Using a variety of stepwise multiple logistic regression techniques, these investigators identified that the alarm features of age greater than 50 years and hematochezia were

independent predictors of lower GI organic disease. Most importantly, they found that symptom-based diagnostic accuracy for differentiating between IBS and organic disease was enhanced when alarm features were considered along with nonalarm features (such as gender and pain frequency and severity) and the Manning criteria.

Additionally, it generally is agreed that any patient older than 50 years of age with IBS symptoms should undergo colonic imaging. The recommendation for colonic imaging in persons over the age of 50 years is predicated largely upon data addressing the prevalence of colon cancer in the general population. IBS symptoms in the absence of warning signs have been associated with a low likelihood of colon cancer. In a recent systematic review, the average age of patients with IBS in studies evaluating the utility of colonic imaging ranged from 39 to 45 years, and the prevalence of colorectal cancer in these studies was low, ranging from 0 to 0.51% [16]. Thus, until comparative data between IBS patients and properly gender- and age-matched controls become available, recommendations for colonic imaging (for the purpose of colorectal cancer screening) in patients over the age of 50 years seems reasonable. Such an approach in younger patients who fulfill IBS symptom-based criteria and do not have warning signs is unlikely to result in a clinically meaningful rate of alternative diagnosis.

In patients with symptoms consistent with IBS who have alarm features, the nature and severity of symptoms and the patient's expectations and concerns will influence the choice of diagnostic testing. Most patients will undergo routine blood and stool tests depending upon their predominant symptoms. With regard to colonic imaging, it is attractive to suggest that patients with diarrhea-predominant symptoms undergo colonoscopy with inspection of the distal terminal ileum to exclude IBD or colon cancer. The necessity of colonic mucosal biopsies in patients with diarrhea-predominant symptoms remains controversial. If a patient has clinical features suggestive of a secretory process, such as nocturnal diarrhea, large-volume diarrhea that is unaffected by fasting or a low fecal osmotic gap (<50 Osm/kg), random colonic biopsies should be performed to exclude microscopic colitis [45]. If laboratory and stool testing suggests the presence of malabsorption, upper endoscopy with small bowel biopsies or testing for SIBO may be warranted.

In patients with constipation-predominant symptoms, the major objective of colonic imaging is to exclude the presence of mechanical obstruction. Colonoscopy can be used for this purpose. Alternatively, particularly in younger patients where the fear of missing small lesions such as polyps is less of a concern, air contrast barium enema can exclude obstructing lesions of the colon effectively and identify colonic dilatation suggestive of pseudo-obstruction/megacolon.

If alarm features are not present, and the patient fulfills symptom-based criteria, a confident diagnosis of IBS should be made, and symptom-directed therapy should be initiated (Fig. 1). A crucial aspect of this approach is

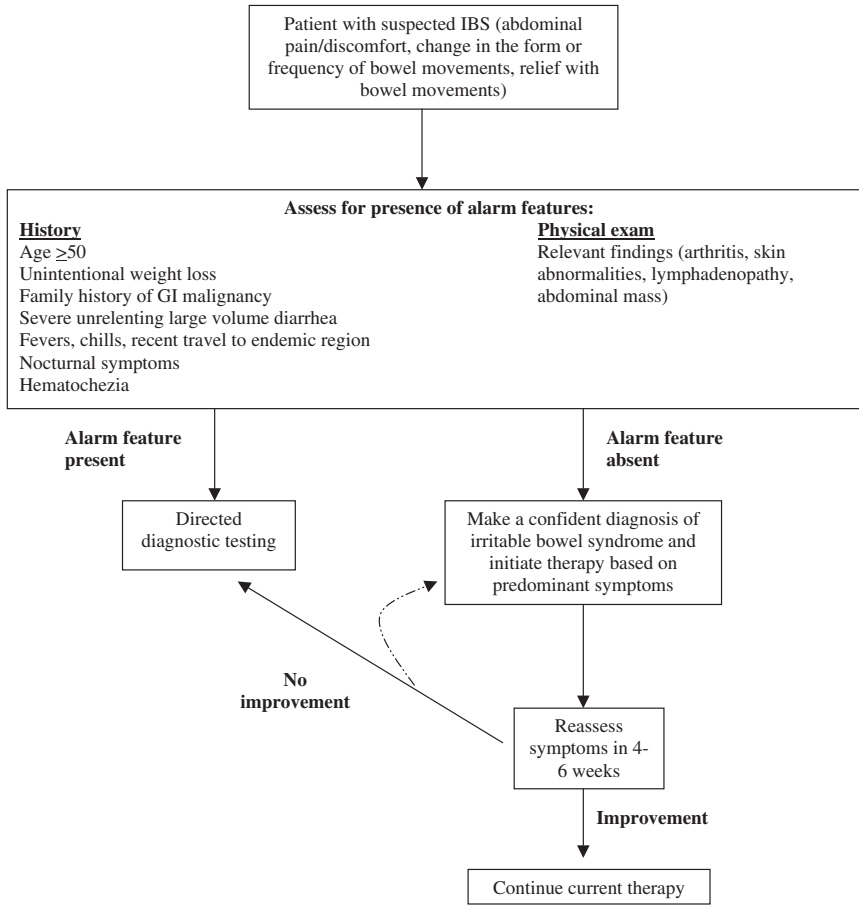

Fig. 1. Approach to the diagnosis of irritable bowel syndrome.

adequate and timely follow-up. If, after appropriate therapeutic interventions, the patient reports no significant improvement, a more extensive diagnostic evaluation may be indicated. With appropriate follow-up, a clinically significant delay in the diagnosis of important organic disease is very unlikely, as demonstrated by multiple longitudinal studies that have demonstrated the durability of the diagnosis of IBS.

Once made, clinicians should be reassured by the durability of the diagnosis of IBS over time. In one study, Yawn et al reviewed the medical records of 149 patients diagnosed with IBS [46]. During 3 years of follow-up, only one (0.67%) patient was diagnosed with an organic disease (IBD) felt to explain the patient's GI symptoms. Owens et al found a similar rate of alternative diagnoses in their cohort of 112 patients diagnosed with IBS [47]. During a median follow-up of 20 years, one (0.89%) patient was given an alternative diagnosis felt to be responsible for the patient's GI symptoms.

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Disturbances of Motility and Visceral Hypersensitivity in Irritable Bowel Syndrome: Biological Markers or Epiphenomenon

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There is no pathological or biochemical definition of irritable bowel syndrome (IBS); this remains entirely clinical and is based either on the recognition of a symptom complex considered diagnostic, or by the exclusion of other diagnostic possibilities. According to Rome II [1], which represents only a minor modification of Rome 1 [2], IBS is defined as follows: at least 12 weeks (which need not be consecutive) in the preceding 12 months of abdominal discomfort or pain that has two of these three features: relieved by defecation or onset associated with a change in stool frequency or onset associated with a change in form or appearance of stool. In reviewing any data on the pathophysiology of IBS, one must be aware of the limitations of this approach to defining IBS; this definition is restrictive and may bias toward certain etiologic mechanisms. Other approaches to definition [3–6] similarly may influence the relative importance of any given pathophysiological mechanism in IBS. For example, the inclusion, within the spectrum of IBS, of patients with unexplained diarrhea will lead to a consideration of factors that may disrupt mucosal transport. Several other issues need to be considered in the evaluation of any study of IBS. These include the location of the study (ie, whether based in the community or in a tertiary referral center) and whether those who overlap with functional dyspepsia and nonerosive reflux disease are excluded. Decisions regarding the latter may appear attractive from a study design perspective but may fail to reflect clinical reality, where overlap is the rule rather than the exception.

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The desirability of treating these functional disorders as a spectrum, rather than as separate and discrete conditions, is emphasized further by several shared characteristics. For example, the common functional disorders, noncardiac chest pain, functional heartburn, functional dyspepsia, and IBS, share a population with similar demographic features and have been characterized by the presence of variable motor abnormalities and visceral hypersensitivity, the subjects of this article, and other phenomena, such as autonomic dysfunction, altered central perception of visceral events, hypothalamic–pituitary axis dysfunction, subtle inflammation, and a significant role for stress and psychological factors. Another important issue in any consideration of the pathophysiology of IBS is its fluctuating nature. The typical IBS patient reports episodes of intense symptoms separated by periods of well-being; for example, one recent study documented that patients with IBS suffered symptoms on an average of 7 days or 14 hours per month [7]. If a motor or sensory abnormality is linked to symptoms, the timing of a study becomes critical. To confuse matters further, symptom expression may vary within the same patient from diarrhea on one occasion, to constipation on another, each of these symptoms being associated with quite different motor changes.

Although the pathophysiology of IBS remains unclear, several factors have been proposed [4,8]. The primacy of any one of these factors has not been established in IBS. It remains entirely plausible to propose that a given factor may predominate in an individual patient; so far, attempts to associate symptom pattern with pathophysiology have proven unsuccessful.

Gastrointestinal Motor Dysfunction in Irritable Bowel Syndrome; is Irritable Bowel Syndrome a Motility Disorder?

Dysmotility long has been considered a major factor in the pathophysiology of IBS, as indicated by the use of such terms as the spastic colon to describe what now is referred to as IBS. Accordingly, it was suggested that gut spasm or other abnormal contractile activities led to the development of symptoms in IBS. There are, indeed, several reports of abnormal motor patterns in many parts of the gastrointestinal (GI) tract in IBS [9,10].

Initially, the focus was on the colon, and several electromyographic and manometric abnormalities were described in early studies. Patients with IBS seemed particularly predisposed to developing colonic dysmotility, often associated with symptoms, in response to food ingestion and on exposure to stressful stimuli. Recent reviews of the literature suggest that there is not good evidence for an abnormality in baseline motor activity in the colon in IBS and that many of the abnormalities described may have been related to associated psychopathology or to the nonspecific effects of associated constipation or diarrhea. With regard to the latter, it is evident that colonic [11–13] and rectal [14,15] motor changes in IBS, may reflect those associated

with the predominant symptom, be it diarrhea or constipation, in a given IBS subgroup. The interpretation of these studies also is complicated by the relatively primitive understanding of normal colonic motility and its intrinsic variability and sensitivity to extrinsic influences [9].

More recently, the emphasis has shifted to the small intestine, where the description of several motor abnormalities generated considerable interest [10,16]. Although most studies of small intestinal motor activity have failed to demonstrate any basic abnormality of the migrating motor complex in IBS [16], several studies have revealed a prominence of repetitive bursts of contractions or clusters [17–19]. Indeed, in some of these studies, the appearance of clusters in the jejunum was accompanied by the onset of the patient's typical symptoms [17,19]. Clusters are not diagnostic of IBS; they are a feature of several motor disorders [10,16]. Furthermore, several other investigators have failed to demonstrate an increased prevalence of clusters among their IBS patients [20–24]. Other abnormalities of small intestinal motor function have been described in IBS, including prominent high amplitude waves in the terminal ileum and an exaggerated jejunal motor response to meal ingestion [17,18]. Whether the presence of clusters and other motor abnormalities in some IBS patients reflects the effects of associated diarrhea, an undue sensitivity to external stress or, indeed, a basic abnormality of the enteric neuro–muscular apparatus remains unresolved. It remains entirely possible that a small number of so-called IBS patients are in reality a part of the spectrum of chronic idiopathic intestinal pseudo-obstruction (CIIP) [16]. In support of this concept are reports of motor abnormalities in some IBS patients reminiscent of CIIP and a very recent description of histological abnormalities in the enteric nervous system of the small intestine in a small number of patients with what was described as severe IBS [25].

Although less studied, disturbances in transit have been demonstrated in IBS. Here again, results are influenced by the nature of the predominant bowel habit [10]. Of particular interest are very recent observations on the handling of gas by the intestine in IBS [26–28]. Sensations attributed to gas are extremely common, distressful, and notoriously difficult to treat in IBS, though the actual production of gas in the intestine has been assumed to be normal [29]. Two recent studies, however, have suggested that colonic fermentation may be increased in IBS [30,31]. Other recent studies suggest that IBS patients may handle gas differently. Whereas gas infused into the small intestine was rapidly evacuated through the gut in normal volunteers, a similar infusion resulted in gas retention, symptoms, and an increase in abdominal girth in patients with IBS [26], all reversible by administration of a prokinetic agent [28]. In normal volunteers, similar sensations can be induced by the voluntary retention of gas [32]. Distension, often the most distressing gas-related symptom in IBS, has, until recently, been assumed to represent a disturbance of perception, as apparently objective tests of abdominal volume failed to detect any increase in IBS [33]. This assumption

has come into question [34], and it may come to pass that more detailed studies of changes in distension over time [35] may detect significant diurnal variations in girth in IBS. It should be noted that, in contrast to studies demonstrating impaired transit of gas, others have reported accelerated transit of a mixed solid–liquid meal in bloated IBS subjects [36]. These issues are reviewed in an article by Azpiroz and Malagelada elsewhere in this issue. Motor abnormalities also have been described in the esophagus and stomach in IBS [10,37]. As evidenced by studies of gastric emptying in patients with IBS and functional dyspepsia, it is clear that many of these reports reflect overlap between IBS and other functional disorders, rather than an intrinsic phenomenon in IBS [38].

What is the clinical significance of disturbed motor function in IBS? First, it seems reasonable to state that some IBS patients will demonstrate disturbances of colonic or small intestinal motor function, if appropriately studied, especially if tested in response to such stimuli as food ingestion and stress. Second, it remains difficult to interpret the significance of these findings because of the possible confounding effects of selection bias and such epiphenomena as stress and psychopathology. The possibility of a fundamental abnormality of enteric neuromuscular function in some IBS patients cannot be discounted; however, it is likely to afflict only a minority. It recently was suggested that small intestinal dysmotility may explain the occurrences of small bowel bacterial overgrowth in some patients with IBS [39]. Finally, regardless of the relevance of dysmotility to the fundamental pathogenesis of IBS, its role in symptom generation continues to be supported by the reported efficacy of some antispasmodic drugs in this disorder [40,41]. It also can be argued that the failure of such agents to provide anything other than transient symptomatic relief during acute flares speaks against the primacy of dysmotility in the pathogenesis of IBS.

Visceral hypersensitivity and hyperalgesia; the ubiquitous phenomena in functional gastrointestinal disorders, including irritable bowel syndrome?

There has been recent interest in these phenomena, not only in IBS, but also in functional disorders in general [42]. The phenomenon of visceral hypersensitivity to distention and other intraluminal stimuli, common to patients with noncardiac pain, functional dyspepsia, and the irritable bowel, appears to demonstrate organ specificity in these various disorders [43]. It was suggested recently that both visceral hypersensitivity [44] and visceral hyperalgesia [45], the phenomenon whereby stimuli normally not experienced as painful become so, is highly specific for IBS. These observations are not new. Thus, many will be familiar with such clinical observations as sensitivity to digital rectal examination, sigmoidoscopy, and colonoscopy among patients with IBS. Indeed, some of the first direct studies of sensory phenomena in IBS were performed, at the time of colonoscopy, by

distending balloons in various parts of the colon [46]. These investigators found that not only did IBS subjects prove more sensitive to distension, but also that they demonstrated a different pattern of pain referral. Thus, whereas in control subjects discomfort and pain elicited by distension tended to be experienced close to the site of distension, in patients with IBS, pain often was referred over wide areas and at a considerable distance from the site of distension, a phenomenon that since has been referred to as viscero–somatic referral. These phenomena, namely, visceral hypersensitivity, visceral hyperalgesia, and viscero–somatic referral have been confirmed in IBS in more recent studies using several methodologies under controlled experimental conditions [45,47–51]. Although visceral hyperalgesia has been postulated as being highly specific for IBS, it alone or in association with other manifestations of hypersensitivity cannot explain all of IBS. Even the most celebrated enthusiasts for the sensory hypothesis concede that sensation is normal in some patients [52]. These detailed pathophysiological investigations have revealed differences not only between normal volunteers and IBS patients, but also between IBS and another challenging patient population, those with functional abdominal pain (FAP). Patients with FAP [53] or other functional GI disorders [44] do not exhibit the same changes in pain threshold to rectal distension and meal-related motor responses as IBS subjects.

There are several possible anatomical locations for sensory abnormalities in IBS, ranging from sensory receptors on the gut wall, primary sensory afferent neurons, the spinal cord, and the brain itself. Research in animal models has enhanced understanding of the mediation of sensory signals from the gut. Research in this area in people is notoriously difficult. Advances in functional brain imaging provided by such techniques as cerebral evoked potentials, positron emission tomography, magnetoencephalography, and functional MRI (fMRI) [54], however, have provided insights into the brain's response to visceral stimuli. Such studies have described variable patterns of cerebral activation in response to visceral stimuli in IBS. For example, Aziz and Thompson characterized their IBS patients by a failure to activate the anterior cingulate gyrus in response to a painful stimulus [55]. Mertz et al, in direct contrast, found a greater intensity of activation of the anterior cingulate cortex in IBS in response to painful rectal distension [56]. These and other studies have advanced the concept of abnormal (or hypervigilant) central nervous system (CNS) perception of visceral events in IBS. Other pieces of evidence support this concept. These include the conscious perception by IBS patients of intestinal motor events that usually are subconscious [57] and evidence of abnormal psycho-neuro-hormonal responses, often implicating an abnormal hypothalamo–pituitary axis [58].

Until recently, it was not possible to use pharmacological agents to test the role of visceral hypersensitivity in IBS. The delineation of the role of serotonin (5-hydroxytryptamine, 5-HT) at a number of levels in visceral

sensation and the development of relatively specific 5-HT_3 and 5-HT_4 receptor agonists and antagonists have permitted some evaluation of the therapeutic potential of this approach. These agents are reviewed in an article by Schoenfeld in detail elsewhere in this issue. There is some evidence that administering these agents provides relatively long-term symptomatic relief for some IBS patients. It also has been postulated that the efficacy of antidepressants and various psychological therapies in IBS may be related, at least in part, to effects on visceral sensation and perception. None of these agents have, however, proved to be a panacea in IBS; whether this observation reflects the heterogeneity of IBS or the nonprimacy of these phenomena in IBS remains to be defined.

That visceral hypersensitivity may be an epiphenomenon in IBS has been suggested by some authorities [59] who propose that, as for motility, these sensory perturbations may reflect the effect of stress and psychological factors associated with, or consequent upon, IBS. This contention is supported by the ability of therapeutic interventions, directed solely at the modulation of the psyche, to modify sensory and motor phenomena in IBS [60–62].

If dysmotility and visceral hypersensitivity are not biological markers, can another unifying hypothesis explain their occurrence and association with symptoms in irritable bowel syndrome?

An extensive literature documents the potential for stress and psychopathology to influence GI motor, sensory, and secretory function, both in the short- and in the long-term. As reviewed in an article by Palsson and Drossman elsewhere in this issue, patients with IBS traditionally have been assumed, on the basis of scanty evidence, to suffer from a variety of psychological disturbances. More recent evidence suggests, on the contrary, that most patients with IBS are indistinguishable from the rest of the population in psychological terms. Psychopathology is a characteristic of a very particular subgroup of this patient population: those who seek medical attention and, in particular, those who seek specialist referral [63]. This is an excellent example of how a failure to account for selection bias can lead to erroneous extrapolations from a highly selected population. This is not to say that depression and anxiety, if present, will not influence the nature and severity of symptomatology in an individual patient. Although it is imperative that one be aware of the possible impact of anxiety, depression, stress [64], and other psychological and psychosocial factors [65] on a host of physiological parameters when interpreting any abnormality described in IBS, it seems unlikely that psychopathology can provide a unifying hypothesis to explain IBS pathophysiology.

The other contender for supremacy as the unifying hypothesis in IBS is that of low-grade inflammation (reviewed in an article by Bercik and

colleagues elsewhere in this issue). Quite apart from the specific issue of IBS, there are several converging strands of evidence indicating the extent to which infection or inflammation can disrupt gut function in people. Some of the best evidence has been extant for decades and illustrates the occurrence of dysmotility as a consequence of a chronic infection, namely, Chagas' disease [66], a disorder that can affect motor function throughout the GI tract through an inflammatory process affecting the myenteric plexus consequent upon either an immune response [67] or chronic persistent infection [68]. The postviral syndromes provide another example of infection-provoked dysmotility [66]. A recent review suggested that, among a large group of patients with idiopathic gastroparesis, about 25% gave a history suggesting viral prodrome [69].

More direct evidence for a role for inflammation in the mediation of motor changes comes from inflammatory bowel disease (IBD). Although motility is known to be disturbed in IBD, it has not been studied extensively, the focus instead being on the inflammatory process, as it affects the mucosa. There is, however, a suggestion that some of the motor abnormalities may persist even when the inflammation resolves. Although this has been shown in just a few studies, it does raise the possibility that these patients could evolve into an IBS-type syndrome during periods of remission of IBD [70]. Chronic inflammation in IBD leads to significant changes in the phenotype of smooth muscle and enteric neurons, to the extent that they can assume immunological functions, leading to a self-perpetuating cycle of interactions between inflammatory cells and the enteric neuro–muscular apparatus [71,72]. There is also evidence to support an infectious role in chronic intestinal pseudo-obstruction [73]. In a very detailed pathological examination of the mucosa and muscularis in patients with pseudo-obstruction, Lindberg et al documented a consistent lymphocytic ganglionitis [74]. Interestingly, these patients also had mucosal inflammation, with increased numbers of intraepithelial lymphocytes and, in some cases, frank inflammation of the mucosa, suggesting a direct and perhaps causative link between mucosal inflammation on the one hand and inflammation of the enteric nervous system on the other. Finally, several reports have associated celiac disease and IBS [75–77].

Real data now are emerging that directly support the concept of postinfective or postdysenteric IBS [78–84]. In one such study among a group of patients with documented bacterial gastroenteritis, 7% had developed symptoms consistent with IBS when followed up 6 months later [79]. Risk factors for postinfectious IBS include being female; having a prolonged initial illness [79]; and higher scores for anxiety, depression, somatization, and neurosis [81,82]. Gwee et al documented several functional abnormalities, including accelerated whole gut transit, decreased rectal threshold for sensation, and abnormal rectal compliance in postinfectious patients [82]. Surprisingly, motor and sensory dysfunction was equally common among patients who had developed IBS and those who had

not, suggesting that these are relatively nonspecific consequences of inflammation.

Although the previous studies examined the consequences of an acute enteric infection on the intestine, others have suggested that there may be more chronic alterations of the enteric flora in IBS. This concept is supported by a symptomatic response to the eradication of small intestinal bacterial overgrowth in IBS [85].

More recently, several studies documented low-grade inflammation, immune activation, and increased mast cell populations in the colon in IBS, not only in relation to a prior infectious precipitant [82,83], but also in unselected patients [25,86–88]. This is of particular interest given the considerable experimental evidence indicating that inflammation can alter gut motor function [89]. In muscle, altered contractility, collagen deposition, enhanced expression of MHC class 2 and ICAM-1, and cytokine production have been documented [89]. In nerves, altered morphology, variable changes in neurotransmitter content, and activation of sensory afferents (perhaps by means of calcitonin gene-related peptide [CGRP]) have been described [89]. These changes have been noted in the context of inflammation limited to the mucosa and even at sites remote from the area of inflammation. Most fascinating is very recent description of close proximity between afferent nerve endings and mast cells in IBS, thus suggesting a direct pathway whereby a luminal stimulus could activate sensory afferents and perhaps mediate hypersensitivity [90,91].

Autonomic dysfunction has been documented with some regularity in IBS [92–94] and has the potential to provide another unifying hypothesis. What remains to be defined, however, is to what extent disturbed autonomic function in IBS is a consequence rather than the cause of IBS.

Pathophysiological hypotheses are not mutually exclusive

In attempting to make sense of current theories of pathophysiology in IBS, it is important to maintain an open mind and to accept the distinct possibility that more than one of these factors may interact in a given patient. The role of psycho–social factors in the predilection to post-infective-IBS is a nice illustration of such an interaction. Insights are being gained into how stress and psychopathology might modulate the inflammatory response [95,96]. Thus, the neurotransmitters, substance P and CGRP, can modulate or initiate an immune response, and stress can exacerbate or reactivate inflammatory responses in animal models and in experimental models. In a genetically predisposed individual, inflammation or diarrhea may sensitize the gut to subsequent stimuli. There is accumulating evidence suggesting that an inflamed gut may be more sensitive through up-regulation of sensory phenomena within the gut wall and in the CNS. Similar interactions may occur between motor activity and sensation. Indeed dysmotility and sensation may not operate in isolation but

be inter-related. For example, Munakata et al demonstrated that the induction of repetitive sigmoid stimulation, in a manner analogous to the sigmoid spasm characteristic of IBS, accentuated the hyperalgesia and increased viscero–somatic referral associated with rectal distension in IBS [97]. Similarly, it stands to reason that alterations in visceral tone and compliance will reset the thresholds for the visceral responses to distension and other stimuli. Gut–brain interactions are bidirectional. Although abnormal perception of gut events may be commonplace in IBS, it is equally possible that brain-initiated stimuli may alter gut motility and tone and adjust peripheral receptors. The lines of communication also may be disrupted, as evidenced by the frequency with which autonomic dysfunction is reported in IBS.

One lesson to be derived from the recent history of IBS research is that it is essential not to examine one aspect of pathophysiology in isolation. Thus, it seems unlikely that one particular theory will explain IBS. The onset of symptomatic IBS most likely represents the convergence of genetic and psycho–social factors, perhaps triggered by some external stimulus such as a dramatic life event or an enteric infection or inflammatory condition. Dysmotility, hypersensitivity, and disturbed brain perception may be the consequences of these events rather than primary abnormalities. That is not to say that these phenomena are irrelevant; they may be the mechanisms whereby symptoms are generated. Therefore, they will continue to be valid targets for therapeutic intervention.

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Is Irritable Bowel Syndrome a Low-Grade Inflammatory Bowel Disease?

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The influence of the immune system on gastrointestinal (GI) function has long been recognized. The work has focused mainly on the effect of overt inflammation on GI motility. Studies in patients with inflammatory bowel disease (IBD) have shown that colonic inflammation reduces basal contractile activity in the distal colon, which, under physiologic conditions, slows fecal stream [1]. Other studies have reported that intestinal inflammation alters responsiveness of the colonic motor system to a meal [2] and to pharmacologic stimulation [3]. Altered motor patterns seem to improve during remissions of IBD [1], suggesting that colonic dysfunction is dependent on the degree of the inflammation. A study in patients with inactive Crohn's disease, however, has shown persistently abnormal small intestinal motility compared with healthy controls, suggesting long-lasting effects of inflammation [4]. Thus, these studies suggest that immune activation and mucosal inflammation alter motility in humans.

The immune system may alter gut function by targeting intestinal smooth muscle cells, nerves, or the pacemaker system (interstitial cells of Cajal). Surgical specimens from the inflamed small intestine of patients with Crohn's disease have demonstrated increased muscle contractility upon carbachol stimulation attributable to changes at the receptor level [5]. In contrast, colonic muscle contractility has been reported to be decreased in patients with ulcerative colitis [6]. Also, gut inflammation has been shown to decrease the response of circular and longitudinal muscle to endogenous tachykinins [7].

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Structural changes in the enteric nervous system (ENS), such as increased number of ganglion cells [8] or axonal degeneration [9], have been documented extensively in IBD. The presence of an inflammatory cell infiltrate [10] and expression of major histocompatibility complex class II molecules in the ENS of IBD patients [11] suggest that these abnormalities involve immune activation. COX-2 expression in neural cells of the myenteric plexus was found in patients with active IBD but not in healthy controls [12], and thus increased prostaglandin synthesis may be one of the mechanisms leading to gut dysfunction. Other studies reported increased substance P content and its receptor in patients with Crohn's disease [13,14]. A recent study in patients with ulcerative colitis described ENS remodeling with a shift from mainly cholinergic to substance P (SP)-positive innervation [15]. Finally, the number of interstitial cells of Cajal (ICCs) has been shown to be reduced in patients with Crohn's disease [16]. In addition to motility disorders, one of the possible mechanisms leading to symptom generation in inflammatory disorders of the GI tract is visceral hypersensitivity. Reports on visceral hyperalgesia in IBD, however, are controversial. Patients with active ulcerative colitis show decreased thresholds for painful and non-painful stimuli when compared with healthy controls or patients with colitis in remission [17,18]. Conversely, an increased threshold for rectal distension has been found in patients with isolated ileal Crohn's disease compared with controls or patients with diarrhea-predominant IBS [19]. A recent study in patients with ulcerative colitis showed that discomfort thresholds during rectal distension are correlated inversely with the activity of the disease. Patients with colitis, however, had higher thresholds to visceral perception than healthy controls and irritable bowel syndrome (IBS) patients [20]. The presence of visceral hyperalgesia in IBD likely depends on disease activity, whether acute or chronic inflammation predominates, and the region involved. Intuitively, different immune or inflammatory cell infiltrates will impose different effects on sensory nerve function—a concept supported by recent preliminary reports in animals [21,22].

Taken together, these studies suggest that in patients with IBD severe inflammation affects all parts of the neuromuscular apparatus, resulting in significantly altered gut function that may persist even during periods of remission.

Irritable bowel syndrome symptoms in inflammatory bowel disease

There is considerable overlap between symptoms in patients with IBS and IBD, and they include abdominal pain and diarrhea. The presence of endoscopically verified colitis, fever, GI bleeding, serologic markers of inflammation, and overt inflammation in biopsies is diagnostic for IBD. In a proportion of patients later diagnosed with IBD, however, initial symptoms may be attributed to a functional gut disorder. A recent study

showed that the prodrome period in patients with Crohn's disease and ulcerative colitis was 7.7 and 1.2 years, respectively. Most of the patients presented with abdominal bloating, diarrhea, excessive gas production, and stomach pain. When Rome I criteria were applied, patients with Crohn's disease who presented with IBS symptoms had a prodromal period of 6.8 years, while patients with ulcerative colitis had a prodromal interval of 2.7 years [23]. Similarly, during periods of remission, IBD patients may present with symptoms resembling IBS, including constipation and bloating. A substantial number of patients with ulcerative colitis in remission reported bowel symptoms highly suggestive of IBS despite no signs of active inflammation [24]. A recent study demonstrated that 57% of patients with Crohn's disease and 33% of patients with ulcerative colitis in long-standing remission, as assessed by laboratory, clinical, and endoscopical parameters, have IBS-like symptoms. Patients with Crohn's disease reported more GI symptoms and reduced well-being than patients with ulcerative colitis. IBS symptoms seemed not to be affected by age, treatment, or extent of the disease but correlated with the duration of the disease [25]. Based on Rome II criteria, another study confirmed a several-fold higher proportion of IBS symptoms in patients with colitis in remission. IBS symptoms were present in 41.7% and 31.5% of patients with Crohn's disease and ulcerative colitis, respectively, but only in 7.6% of healthy controls [26].

These findings are consistent with the hypotheses that subclinical inflammation and immune activation that precede the expression of IBD result in symptoms of IBS and that previous immune activation and inflammation are followed by gut dysfunction and the generation of IBS symptoms.

Degree of inflammation, gut function, and symptom generation

Diagnosis of active IBD requires the presence of macroscopic inflammation, polymorphonuclear and mononuclear cells, and epithelial damage in biopsies. The severity of the disease, however, does not always correlate with the severity of symptoms reported by patients [27]. Abdominal pain and diarrhea are also frequent symptoms in microscopic colitis, which is characterized by only a mild increase in intraepithelial lymphocytes and monocytes.

The question arises, what degree of gut inflammation is necessary to affect gut function? Gut function may be altered by low numbers of inflammatory cells positioned at strategic locations such as in proximity of enteric nerves. It is beginning to be recognized that an intact epithelium in the absence of mucosal inflammation does not exclude the presence of inflammation in deeper layers of the gut that can result in altered gut function [28].

The availability of more sensitive techniques to assess inflammation such as immunohistochemistry or molecular methods may result in a new definition of inflammation in the gut. The transition between mild immune

activation and gut inflammation is a continuum, and setting an arbitrary threshold between these two entities may be artifactual and eventually misleading.

Low-grade inflammation and irritable bowel syndrome

There is growing evidence that previous infection and persistent low-grade inflammation play an important role in the pathogenesis of gut functional diseases. A large epidemiological study has identified infectious gastroenteritis as the most significant environmental risk factor for the development of IBS [29]. IBS symptoms have been reported to develop in a significant proportion of subjects with documented *Campylobacter*, *Salmonella*, *Escherichia coli*, *Shigella* infections and viral infection [30–33]. Although rates differ among these studies, the estimates range from 7% to 31% of infected subjects. Several risk factors for subsequent IBS development have been identified, the strongest being the duration of diarrhea during enteritis [34], which could reflect the severity of the initial inflammation.

Results of several studies suggest that symptoms in postinfective IBS are generated or maintained by immune mechanisms. Increased intraepithelial lymphocytes (IEL) and lamina propria lymphocytes, together with elevated numbers of enteroendocrine cells, were found in patients with postinfectious IBS, following documented infectious enteritis. These changes in mucosa persisted for at least 1 year and were accompanied by increased mucosal permeability [35]. A small but significant increase in lamina propria lymphocytes, compared with healthy controls, also was observed in patients with postinfectious IBS 3 months after infection [36].

Interleukin (IL)-1β mRNA expression was higher in rectal biopsies in patients with enteritis who subsequently developed IBS, than from those patients whose bowel normalized thereafter. Levels of IL-1β further increased 3 months after infection in patients with IBS, while asymptomatic subjects had similar levels to healthy controls [31]. As IL-1β is a proinflammatory cytokine, these findings are consistent with the hypothesis that subjects who subsequently develop IBS after infection inefficiently downregulate acute inflammatory responses. Support for this concept of impaired control of cytokine production in subsets of IBS patients has gained support from recent genetic studies in IBS. A recent study confirmed increased IL-1β levels, structural changes in enteric nerves, and increased mast cell counts in biopsies from patients with postinfectious IBS [32]. Patients with postinfectious IBS also may exhibit a cytokine imbalance favoring proinflammatory cytokine IL-12 versus counterinflammatory cytokines IL-10 and transforming growth factor (TGF)-β [37].

The immune system also may play a role in generating symptoms in patients with IBS and no history of GI infection. Chadwick et al found that most patients with insidious onset of IBS symptoms showed signs of immune activation as assessed by immunohistochemistry. From these

patients, 49% had normal conventional histology, and 40% had only microscopic inflammation, consisting of increased lamina propria cellularity, often accompanied by focal neutrophil infiltration. By using immunohistochemistry, a twofold increase in IEL and CD3 + cells and a sixfold increase in CD25 + cells were demonstrated. A subgroup of patients also had elevated numbers of neutrophils and mast cells [38]. This is in accordance with another study in IBS patients with or without history of previous gastroenteritis where increased numbers of lamina propria lymphocytes and mast cells were found [39].

Immune activation or inflammation in the mucosa also may affect the deeper layers of the gut. A study on full-thickness biopsies from patients with severe IBS revealed intra- and peri-ganglionic infiltration by lymphocytes at the region of the myenteric plexus [28]. Less than half of the patients had concomitant elevation of intra-epithelial lymphocytes, however, suggesting compartmentalization of the gut for immune processes. Almost all patients exhibited a thickening of the longitudinal muscle layer, and half of the patients displayed abnormal numbers or morphology of ICCs. This suggests that significant inflammation can be present in the deeper layers of the gut with apparently normal mucosa and that this inflammatory process can affect all the elements of the neuromuscular apparatus.

A recent study investigated the role of mast cells in IBS. The authors found that most of the patients had increased areas of mucosa occupied by mast cells, higher numbers of degranulating mast cells, and increased release of histamine and tryptase from biopsies than healthy controls. Furthermore, the abdominal pain or discomfort correlated with the number of mast cells located in close proximity to the enteric nerves [40]. Mast cells could be among the effector cells responsible for immediate-onset symptoms. This would suggest that luminal antigen plays a role in maintaining symptoms in IBS.

The data from these studies suggest that infectious gastroenteritis is an important trigger in at least a subset of patients with IBS. The authors propose that an activated immune system is responsible for maintaining symptoms. There is also evidence that immune mechanisms may be implicated in the pathogenesis of patients without history of gastroenteritis. Lymphocytes and mast cells are candidate effector cells involved in symptom generation.

Increased susceptibility to inflammation in irritable bowel syndrome and inflammatory bowel disorder

This article has mentioned that IBS and recent-onset of IBD may share some clinical similarities. Is there any evidence for a common pathogenetic pathway? There are reports suggesting that a common genetic background for IBD and IBS exists based on abnormalities within the immune system.

IL-10 is a pleiotropic cytokine with counterinflammatory properties. It has been shown that mice deficient in IL-10 develop spontaneous enterocolitis [41]. A recent study suggested that patients with IBS may be genetically predisposed to produce lower amounts of this anti-inflammatory cytokine [42]. This is similar to what has been described in patients with IBD [43]. In another study investigating the cytokine pattern in patients with post-infectious IBS, a higher frequency of tumor necrosis factor (TNF)-α intermediate phenotype with increased production of this proinflammatory cytokine was found [44]. TNF-α polymorphism also has been found in patients with IBD [45,46]. These studies suggest that patients with IBS and IBD may have a genetic predisposition to mount an increased proinflammatory response to luminal stimuli and have a decreased ability to down-regulate already existing inflammatory processes. It is possible that the degree of this alteration determines in part the clinical outcome.

Psychosocial factors in irritable bowel syndrome and inflammatory bowel disease: effects through the immune system

Psychosocial factors contribute to the predisposition, precipitation, and perpetuation of IBS symptoms [47]. Comorbidity of psychiatric conditions is high and occurs in up to 94% of patients [48]. Research in the field of psychosomatic medicine showed an association between depression and activation of the immune system [49] as recently documented by elevated C-reactive protein levels in patients with depression [50,51]. Depression also was found to be important predictor for developing postinfectious IBS [36]. Psychiatric conditions and IBD often coexist [52], and it has been suggested that depression and anxiety precede onset of IBD [53]. Recent prospective studies showed a significant correlation between depression and total number of relapses of colitis [54] or disease activity in IBD patients [55]. These data suggest that psychological factors play an important role in the expression of IBS and IBD. Activation of the immune system may be the common pathway mediating behavioral-induced changes in these conditions.

Experimental models of functional gut disorders

Animal models are valuable for investigating the role of intestinal inflammation in gut dysfunction. NIH Swiss mice infected with the nematode *Trichinella spiralis* developed muscle hypercontractility in vitro, which persisted long after parasite eviction [56]. This process was initiated by mucosal Th2 cytokines and maintained by COX-2 [57] and TGF-β [58] in the muscle layer. Previously infected mice displayed abnormal small bowel motility in vivo, with increased retroperistalsis and heightened visceral sensitivity [59]. Although conventional histology and myeloperoxidase were

normal in the postinfective state, increased numbers of CD3 + cells were found in the gut. It should be pointed out, however, that the mucosal compartment was otherwise unremarkable in its appearance. Abnormal muscle contractility normalized when the previously infected mice were fed probiotic bacteria, which also decreased COX-2 and regulated on activation, normal T expressed an secreted expression in the intestine [60].

Abnormal stomach function including delayed gastric emptying, impaired sensitivity to distension with up-regulated SP and calcitonin-gene related peptide-containing nerves, and abnormal feeding behavior developed in mice chronically infected with *Helicobacter pylori* [60,61]. Most of these changes persisted for at least 2 months following bacterial eradication. The degree of neuromuscular impairment, evidenced by acetylcholine release upon EFS, correlated with the degree of mononuclear cell infiltration.

Altered gut function also was observed in rat models of colitis showing abnormal motility, even in the uninflamed segment [62], and increased visceral sensitivity. Postinflammatory hyperalgesia can be observed as long as 17 weeks after induction of the trinitrobenzene sulfonic acid colitis [63]. These studies show that experimental inflammation can induce abnormal gut function, including dysmotility and visceral hyperalgesia, which can be long-lasting.

What drives immune activation and inflammation in functional bowel disorders?

Most patients with GI infection recover without any long-term consequences, restoring their bowel function after few weeks of the initial infection. A small proportion of patients continues to experience chronic problems, however, and the question arises what drives their symptoms that can sometimes persist for up to 6 years after infection [64]? A genetic predisposition to increased susceptibility to inflammatory stimuli may underlie some cases. Environmental factors also should be considered. The gut is exposed continuously to a variety of bacterial and dietary antigens. Immune tolerance toward these antigens assures normal functioning of the gut. During gut infection and inflammation, tolerance is abrogated, and the mucosal immune system may be sensitized toward one or more antigens related to the offending agent. As some patients with IBS have increased intestinal permeability [35], it is likely these patients are exposed to a broader array of luminal antigens, which through molecular mimicry could maintain immune activation. To test this hypothesis, the authors repeatedly administered crude *Trichinella spiralis* antigen to mice that had recovered from this nematode infection. Antigen-fed mice maintained abnormal gut motility and colonic hyperalgesia for 2 months after infection, while mice receiving placebo normalized gut function [59]. Similarly, mice

previously infected with *H. pylori* had slower gastric emptying when gavaged with *H. pylori* antigen compared with placebo-fed controls [61]. In both experiments, the abnormal gut function was accompanied by mild but significant increase in CD3 + cells in the gut wall. These results provide proof of concept that symptoms in patients with IBS could be maintained by the exposure of the gut to the relevant bacterial or viral antigens, or even to dietary antigens, which cross-react with the epitopes of the infectious agent.

Is irritable bowel syndrome a mild form of irritable bowel disease?

The authors believe that IBD and at least a subset of IBS patients exist at two ends of the same spectrum of pathophysiology, which involves immune activation and inflammation. This is prompted by the observation that IBS symptoms may precede IBD, which reflects gut dysfunction generated by subclinical inflammation. It also has been observed that IBS occurs in patients in remission from IBD. This concept is underpinned by results of basic scientific studies in animal models showing that immune activation and inflammation restricted to the mucosal compartment result in profound changes in neuromuscular function that may persist after recovery of the mucosa. Emerging evidence shows similarities in genotype between IBD and a subset of IBS patients; polymorphisms of genes that encode cytokine secretion may result in an imbalance of pro- and counter-inflammatory signals. This in turn would lead to inefficient down-regulation of inflammatory responses and promote low-grade inflammation. It is a matter of the severity of inflammation that separates IBD and this IBS subset, and this may reflect additional genetic abnormalities or greater exposure to environmental factors in the case of IBD. This prompts the question as to whether IBD is more common in patients with IBS, and there is some evidence to support this [65]. Clearly in IBD the brunt of immune-mediated injury is borne by the mucosal compartment, whereas in IBS, the mucosal compartment may play a role in initiating events, but the brunt of injury is taken by the deeper neuromuscular tissues. Further work is required to elucidate differences in the regulation of immune activity between these compartments to better understand the relationship of IBD and IBS.

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The Role of Food Intolerance in Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder, affecting approximately 10% to 15% of the worldwide population [1]. Perhaps because it is so prevalent, IBS sometimes is viewed as a trivial disorder; however, in severe cases, the illness can result in significant disability and impairment in patient quality of life [2]. Although gastroenterologists spend a large proportion of their time dealing with IBS, most patients are seen in primary care, and a substantial proportion does not seek health care at all [3].

In spite of growing interest and research into IBS over the last 20 years, the underlying cause of the condition remains unknown. IBS is almost certainly a multi-factorial illness with particular factors being of paramount importance in certain individuals. These include: motility, visceral sensitivity, central processing, genetic factors, psychological factors, inflammation, and dietary factors. From the patient's perspective, however, the most frequently perceived cause for symptoms is food intolerance. This is perhaps not surprising, given the work by Ragnarsson et al, which suggested that in the region of 50% of patient's pain episodes worsen in the postprandial period [4]. This study also suggested that pain was exacerbated more frequently by food ingestion than relieved by defecation, the latter characteristic being one of the requirements for a diagnosis of IBS according to the Rome II criteria [5]. Probably as a result of these sorts of observations, approximately 60% of patients with IBS think that they have some form of dietary allergy and hence nearly always want to discuss the role of food in their condition [6].

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The importance of the cephalic response to food

Before discussing dietary manipulation, it is important that the patient understands the cephalic response to food, which was demonstrated by Rogers et al in 1993 [7]. These investigators showed that the discussion of food, the smell of food, or even sham feeding led to increased colonic motor activity, thus demonstrating that gut activation can take place even before any food is ingested [8]. Given that increased colonic motor activity has been shown to be associated strongly with abdominal pain in patients with IBS, it is important to realize that the process of eating, irrespective of what is eaten, may exacerbate the symptoms of IBS [8].

Dietary fat, fiber, and other factors influencing gut motility

The most common form of dietary advice offered to patients with IBS is to increase their intake of fiber; indeed a recent survey reported that approximately 95% of general practitioners believe that fiber deficiency is the main cause of IBS [9]. Some years ago, the authors assessed the efficacy of fiber supplementation in treating IBS by recording patients' overall symptomatic response to several sources of dietary fiber [10]. In this, study cereal fiber made 55% of patients worse, with only 11% claiming an improvement. Other forms of fiber were not so deleterious but nevertheless seldom led to an improvement in symptoms. It should be pointed out that this study was undertaken in secondary care patients; thus it could be argued that patients responding well to dietary fiber in a primary care setting would not need to be referred onwards to secondary care and therefore only patients failing to improve, or being made worse by fiber may have entered the study, resulting in selection bias. The authors recently addressed this issue by examining the response to fiber in 100 consecutive primary care IBS patients and found significant differences compared with patients seen in secondary care. In this second study, only 22% of primary care patients reported symptom deterioration with bran, and 27% reported an improvement (R. Lea, Miller, P.J. Whorwell, unpublished data).

In the secondary care setting, the authors therefore give patients a diet sheet recommending cereal fiber exclusion, and this certainly leads to improvement in a substantial proportion of subjects. It is also worth bearing in mind that coffee may act as a colonic stimulant and can upset some patients; hence a period excluding coffee or caffeine containing products is also worthwhile of consideration [11,12]. Dietary fat is another potent modulator of gut motor function. This has been shown by Serra et al, who conducted a series of studies that demonstrated that in contrast to healthy volunteers, IBS patients exhibited retention of gas that had been infused into the small intestine [13]. Following administration of enteral fat, the volume of retained gas increased from 289 to 505 mL [14]. These studies may help to explain the common clinical experience of patients reporting that meals high

in fat exacerbate symptoms, particularly bloating [11]. This is important, because some patients may erroneously conclude they have intolerance to a food such as milk when in fact it is the fat, rather than the milk protein that is causing problems. In a similar way, mashing potatoes in butter can lead to the conclusion that potatoes are a problem when it is the fat in the butter that is actually causing symptom deterioration. It is also essential to appreciate that other aspects of lifestyle may affect gut motility and therefore be implicated in exacerbation of IBS symptoms. For instance, breakfast is a significant stimulant to the gastro–colonic response, and forgoing this meal can exacerbate constipation. Furthermore missing meals and eating irregularly also seem to aggravate symptoms.

Food intolerance and exclusion diets

In 1982, Alun-Jones et al reported evidence favoring the presence of food intolerance in a large proportion of patients with IBS and claimed that by adopting a strict exclusion diet followed by sequential reintroduction of foods, approximately one third of patients would improve [11]. It should be noted, however, that all these patients had diarrhea-predominant IBS and that other studies have not always been able to confirm such a high response rate with this approach. The literature recently was summarized by Niec et al, who performed a systematic review of clinical trials using food elimination diets followed by rechallenge [15]. Of the seven studies included in their analysis, the response rate varied from 15% to 71%, with the higher figures relating to studies of patients with diarrhea-predominant IBS. Milk, wheat, and eggs were the most frequently implicated foods. Although the principal of food elimination or exclusion appears straightforward, for the patient, it is very demanding and is supervised best by a suitably qualified and enthusiastic dietician, because a major disadvantage of dietary elimination is that it can result in a wide range of foods being excluded. Although this would have to be taken to extremes for significant nutritional problems to develop in previously well-nourished individuals, there is a danger of exacerbating hitherto unrecognized underlying eating disorders, resulting in clinically significant malnutrition. This is particularly important, as some years ago the authors showed that a significant proportion of patients with IBS have a predisposition toward eating disorders.

Food allergy and irritable bowel syndrome

IgE-mediated food allergies are rare in adults and typically occur shortly after the offending food, usually nuts, shellfish, or fish, is ingested [16]. Symptoms of abdominal pain, vomiting, and diarrhea, often associated with extra-GI problems such as urticaria, wheezing, or even anaphylaxis, are characteristic. Because they may be potentially life-threatening the

possibility of an IgE-mediated food allergy, in the appropriate clinical context, should not be overlooked, especially in a patient with a personal or family history of atopic disorders.

True food allergy has not been well studied in the much more common clinical setting of IBS. On the occasions when is has been studied, it predominantly has been investigated using IgE-mediated skin prick or radioallergosorbent test (RAST). Petitpierre et al used these methods in 12 atopic and 12 nonatopic individuals who were given an exclusion diet with subsequent food provocation [17]. Fourteen of the 24 subjects responded to food elimination and suffered typical IBS symptoms on dietary rechallenging, with an IgE-mediated mechanism considered likely in nine of the atopic individuals. Thus although food allergy is unlikely to explain symptoms in most patients with IBS, this mechanism may be important in the subgroup of patients with atopy. Although the obvious treatment for these patients is dietary elimination, in practice it may be difficult to determine the offending food and even more difficult to completely remove all traces of it from the diet. To address one possible solution to this problem, Stefanini et al conducted a 4-week multi-center study comparing the efficacy of the mast cell stabilizing agent sodium cromoglycate at 1500 mg per day with an elimination diet and reported that 67% of patients improved with cromoglycate, compared with 60% using the elimination diet [18]. Thus sodium cromoglycate taken before each and every meal may be worth trying in patients suspected of having food allergy and having difficulty with dietary elimination.

In contrast to IgE, IgG antibodies to food are common in the normal population and often have been considered physiological; therefore their potential role in IBS had not been studied previously. In a recent randomized controlled trial, the authors assessed the effectiveness of a food elimination diet based on the presence of IgG antibodies for treating patients with IBS [19]. One hundred and fifty patients were randomized to receive either a true diet based on the patient's individual food antibody profile or a sham diet excluding a similar number of foods, but not those to which they had antibodies. Participants remained on the diet for 12 weeks and were then observed during a 4-week food reintroduction phase. As can be seen from Fig. 1, which compares symptom severity scores in the two groups of patients fully adherent to the diet, patients receiving the IgG-determined elimination diet improved significantly more than those receiving the sham diet. Global rating scores also showed significant improvements, and patients on the true diet suffered far greater deterioration in symptoms than the sham diet group when the diet was relaxed. The foods to which patients were most likely to have antibodies were yeast, milk, egg, wheat, cashew nuts, peas, almonds, and barley. The mechanism by which IgG food antibodies could be mediating this detrimental effect in IBS is unclear; however, in view of mounting evidence to support a low-grade inflammatory process in some patients [20], it is tempting to speculate

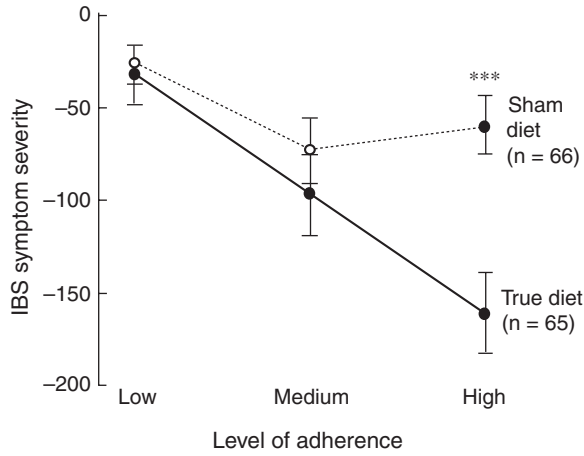

Fig. 1. Symptom severity scores.

that IgG antibodies could be involved in this process. Ultimately, whatever the underlying mechanisms, this study suggests that further research in the area is warranted.

Carbohydrate malabsorption

The role of carbohydrate intolerance in IBS has been addressed by several investigators [21–28]. One representative study measured breath hydrogen and GI symptoms following oral administration of lactose, fructose, sorbitol, and sucrose in 25 patients with functional bowel disorder and 20 healthy volunteers [21]. An elimination diet based on the results of these tests then was implemented. Malabsorption of at least one sugar occurred in 90% of all subjects, although symptom scores were significantly higher in the IBS patients compared with volunteers, and 40% of the patients improved following elimination of the offending sugar. Therefore, while there is evidence that fructose, lactose, and sorbitol malabsorption are all common in IBS patients, malabsorption of these sugars is similarly prevalent in healthy volunteers [21–23,25,26,29–31]. Nevertheless, restriction of carbohydrates in subjects with IBS does seem to help improve symptoms. Thus this approach is worth considering, especially in view of the increasing use of sugar substitutes by food manufacturers. An interesting example of this issue is the use of small quantities of sorbitol in chewing gum, which is sometimes implicated as a cause for symptoms by patients with IBS. Although this may indeed, in part, be related to the presence of sorbitol in the gum as has been discussed, the act of chewing itself stimulates GI motor activity, and this also could result in exacerbation of symptoms [7].

Probiotics

The potential beneficial effects of probiotics are being investigated in a several diseases, and IBS is no exception. The main probiotic bacteria are *Lactobacillus, Bifidobacterium,* and some nonpathogenic forms of *Escherichia coli*. The capacity of these bacteria to adhere to the mucosa seems to be therapeutically important [32], and, by definition, they are all living organisms and therefore need to be able to survive the acidic gastric environment following ingestion to confer any benefit. Initial studies in IBS have been conflicting. Two randomized controlled trials that administered *Lactobacillus plantarum* or placebo to patients with IBS reported a reduction in either flatulence or pain and better overall GI functioning [33,34], although another trial examining the efficacy of this organism failed to demonstrate any effect over placebo [35]. A further study, using the patented probiotic formulation (VSL#3), suggested that although there were no differences in global relief scores, there was a tendency for bloating to improve [36]. An additional study that used tablets containing *Lactobacillus GG* also demonstrated little benefit [37]. One potential reason for these contradictory findings is the vast range of probiotic species available, which probably all vary in their therapeutic potential and degree of adherence. Thus failure of one organism to have an effect does not necessarily imply that this approach is doomed to failure. This view is supported by the preliminary report of a newly identified strain of *Bifidobacterium* appearing to have a promising effect in IBS [38].

Celiac disease

There has been interest recently in the potential overlap between celiac disease and IBS. The prevalence of celiac disease in the population is approximately 0.2% to 0.3%, and recent reports have indicated that this figure may increase to between 10% and 20% in patients with IBS [39–41]. It is possible, however, that this particular subgroup of IBS patients simply may represent a cohort of misdiagnosed patients with celiac disease. To address this issue, it would be helpful to know the prevalence of IBS in patients diagnosed with celiac disease who are adherent to a gluten-free diet, and also to know whether treating celiac disease improves IBS symptoms [42]. It is also important to remember, as has been discussed, that wheat fiber intolerance has a high prevalence in patients with IBS, and therefore benefit from a gluten-free diet may be caused by wheat fiber exclusion rather than gluten withdrawal. With the role of inflammation in IBS becoming increasingly topical, it is interesting to note that patients with inflammatory bowel disease in remission have a higher prevalence of IBS symptoms [43,44]. Thus it might be anticipated that patients with celiac disease in remission also might be affected similarly. There is now debate surrounding the whole issue of screening patients with IBS for celiac disease [45,46] and

whatever the effect on symptoms of a gluten-free diet, there is benefit to be gained in reducing the risk of complications such as osteoporosis and malignancy in treating IBS patients diagnosed with celiac disease.

Summary

Irritable bowel syndrome patients frequently believe that food intolerances are to blame for many of their symptoms, although not uncommonly this is caused by the nonspecific increase in gut motility that occurs with food ingestion. Nevertheless, dietary manipulation may result in substantial improvement in IBS symptomatology provided it is individualized to the particular patient. By further understanding the mechanisms involved in dietary intolerance, it should be possible to optimize the benefits of this approach to treatment.

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GASTROENTEROLOGY
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The Pathogenesis of Bloating and Visible Distension in Irritable Bowel Syndrome

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Bloating is the most frequent and bothersome abdominal complaint reported by patients with irritable bowel syndrome (IBS), and it impairs quality of life even more than abdominal pain [1,2]. Although bloating is very common, it is a term not easily defined. To some individuals, bloating represents a subjective sensation of fullness or pressure inside the abdomen. To others, bloating means abdominal distension, and this complaint often is voiced by women who feel their figure is becoming distorted as the day goes on and clothes do not fit well. Other individuals refer to bloating as a combination of unpleasant abdominal fullness and visible distension.

It is therefore not easy to define pathophysiologically what constitutes bloating, because the mechanisms of disturbed sensation may be different from those that distend the abdomen. One point is agreed by all patients: bloating does not mean fatty accumulation in the abdomen, even though it is known that recent weight gain increases the probability of developing bloating, particularly in females [3]. The main difference between bloating and obesity is simple: bloating varies over time, often from morning to evening, days to weeks, whereas overweight is relatively stable.

In discussing the pathogenesis of bloating, one first must deal with mechanisms of distorted sensation, second, with mechanisms of physical intra-abdominal expansion, and third, with mechanisms of abdominal wall adaptation to content and deformation.

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Mechanisms of distorted sensation

The bloating sensation may arise from a hypersensitive abdominal wall that produces a sensation of increased abdominal tension perceived by the patient as bloating. This mechanism could be the case in abdominal traumatisms, neuritis, or scars. Alternatively, the sensation may originate from abdominal viscera, as is probably the case in patients with functional disorders, in whom normal stimuli within the gut may be perceived as bloating. Indeed, visceral hyperalgesia has been described in patients with functional dyspepsia and IBS [4], and in them, certain standardized intraluminal stimuli replicate their customary symptoms, including bloating.

Several studies have attempted to define regions of the gut and specific pathways affected in different subsets of patients, and there seems to be region specificity [5]. It originally was described that patients with IBS have increased sensitivity in the large bowel, but later studies have demonstrated that the small bowel also is affected [6]. Studies using mechanical stimuli or transmucosal nerve stimulation have shown that patients with IBS have a form of small bowel hypersensitivity that selectively affects mechanosensitive afferents, without disturbing normal perception of electrical stimulation [6]. In patients with functional dyspepsia, which frequently overlaps with IBS, the hypersensitivity affects predominantly the stomach. It has been shown that patients with postprandial bloating have increased perception of gastric distension, which reproduced the customary bloating sensation, whereas perception of duodenal did not [7]. Furthermore, a region-specific replication of customary symptoms has been shown by applying selective fundic and antral distensions in subgroups of functional dyspepsia. In a group of patients with postprandial bloating-related symptoms, fundic distension reproduced the customary symptoms, whereas in patients with ulcer-like pain during fasting, their symptoms were replicated better by antral distension [8].

In patients with functional gut disorders, abdominal bloating may be related to visceral hypersensitivity, but neither the mechanism nor the level of the afferent dysfunction has been established. Visceral afferent input is modulated by several mechanisms operating between the gut and the brain, and conceivably, an alteration of these mechanisms could result in bloating sensation. The tolerance of mechanical stimuli in the gut depends on muscular activity and compliance. For instance, intraluminal gas is tolerated better within the colon than within the poorly compliant small bowel [9]. Furthermore, the perception depends on the length of intestine exposed to a distending stimulus, that is, on the number of receptors activated. It has been shown that summation phenomena may increase gut perception substantially in people [10]. Moreover, summation effects are similar whether adjacent or distant fields are stimulated, and this would explain why a focal collection may be unperceived, whereas pooling of intestinal contents, even at distant sites, may induce bloating. Visceral perception also

is modified by the interaction of different stimuli in the gut [11,12]. For instance, intestinal lipids, frequently related by patients to postprandial bloating, increase the sensitivity of the intestine to mechanical stimuli, and this effect is attributable to sensitization of mechanoreceptors [12].

The autonomic nervous system that regulates gastrointestinal (GI) function also modulates visceral sensitivity. Increased sympathetic tone is known to increase the level of perception of gut stimuli [13]. Some data indicate that patients with IBS have increased sympathetic activity, and hence, this mechanism may play a role in bloating. Visceral perception also is known to be mediated at a cortical level and therefore may be influenced by cognitive mechanisms. Indeed, mental attention has been shown to increase perception to gut stimuli [14], and this finding raises the possibility that patients with bloating may just be paying more attention to what is going on in the gut.

Mechanisms of physical abdominal expansion

The potential elements include adipose tissue (solid), fluid (endoluminal, intravascular, intraperitoneal), and endoluminal gas. As discussed previously, fat accumulation associated with weight gain is unlikely to be accepted by the patient as an explanation of bloating. Likewise, ascitis, even with rapid accumulation, rarely motivates complaints of bloating, and the cause of abdominal distension usually becomes obvious with an appropriate physical examination or diagnostic tests.

Abdominal bloating and distension may arise when tissular water content increases, as may occur with vascular ingurgitation and visceral edema. Such mechanism could play a role in menstrual bloating and other situations associated with neurohormonal or immunological disturbances, but this possibility remains speculative.

Of the remaining putative culprits, endoluminal fluid accumulation seems like a plausible candidate. Indeed, under some circumstances, such as acute diarrheal conditions and in some cases of postprandial bloating, increased volume of intraluminal liquid content may become an important cause of bloating. Reports on small bowel transit of chyme in IBS patients are controversial, however [15,16]. Likewise, data on chyme transit through the ileocolonic junction, an area with sphincteric function, seem equally inconsistent [17,18], although a relation between symptoms and arrival chyme into the cecum has been reported [16]. Uncontrolled observations in the authors' laboratory suggest that intestinal infusion of nutrients may reproduce the typical bloating sensation in some patients. These patients who complain of postprandial bloating may differ from those with typical dyspepsia and IBS, but further studies are needed before firm conclusions can be reached. The deleterious effect of fiber on bloating may be related to the luminal overload. Accumulation of fecal content also may contribute to bloating, particularly in patients with constipation. It has been shown that

bloating improves in constipated patients after laxative treatment, and conversely, bloating can be induced in healthy subjects by loperamide-induced constipation [19]. Other patients, however, tolerate fecal retention without abdominal symptoms, and a different tolerance may be related to colonic compliance and sensitivity.

The third element, gas, is a plausible candidate in most instances of bloating, but the issue is not as simple as it may seem at first glance. For one, the notion that bloating and flatulence are interchangeable manifestations of the same problem is not supported by experimental evidence. Lactulose is a nonabsorbable sugar that is fermented into the colon, releasing hydrogen, and when administered to healthy subjects induces flatulence, sensation of rectal gas, and sometimes bloating. Administration of fermentable (psyllium) or nonfermentable fiber (methylcellulose) to the same subjects did not increase hydrogen production (measured by breath test) and did not produce flatulence or rectal gas sensation. Still, it did induce the sensation of abdominal bloating [20]. Hence bloating sensation likely was related to the intraluminal mass increment produced by the fiber loads, rather than to increased gas production.

Gas production in the human gut is determined by two main factors: the amount of fermentable foodstuffs that remain unabsorbed in the small bowel and enter the colon, and the individual characteristics of the colonic flora. Thus, it is not surprising that bloating is a common clinical feature of malabsorption disorders in which excessive amounts of unabsorbed substrates are fermented in the colon. Along the same lines, when bacterial overgrowth occurs in the mid- and upper small bowel, abnormal fermentation of foodstuffs occurs before full digestion and absorption take place. Whether in intestinal malabsorption or in bacterial overgrowth, bloating and other gas symptoms usually accompany other manifestations, however, and rarely present as predominant bloating. Whether some degree of nutrient malabsorption plays a role in patients with functional bloating remains controversial. Interestingly, even individuals with proven lactose deficiency may tolerate up to 250 mL of milk without symptoms [21]. Some studies suggest that patients with IBS have a reduced absorption capacity of certain substrates in the small bowel [22–24], but this is not a consistent finding, because other studies report discrepant results [25,26]. Investigation of the effect of exclusion diets on bloating also has yielded inconclusive results [27]. Levitt et al produced a series of seminal studies 30 years ago, measuring intestinal gas production by means of an original technique [28]. The gas present in the gut was washed out by a high infusion rate of argon. The anal effluent then was collected and analyzed. With this technique, the volume and composition of intestinal gas was similar in healthy subjects and IBS patients. Furthermore, once a steady-state equilibrium was achieved, the volume of endogenous gas recovered reflected the actual production of gas in the gut, which was also similar in patients and controls, both during fasting and after meal ingestion [29,30].

Breath tests provide a convenient and noninvasive method of measuring intestinal gas production. Intraluminal gases with high diffussibility, such as hydrogen and methane released during colonic fermentation, are absorbed and carried to the lungs, where they pass into alveolar air and finally are excreted by breath. Unfortunately, the results of various studies performed with this methodology are discrepant. In one study, no differences in breath hydrogen concentration measured over 1 week were detected between healthy controls and IBS patients, although patients complained of significant bloating [31]. A second series of studies measured breath hydrogen after administration of lactulose, a nonabsorbable fermentable sugar, and showed, first, that a high proportion of patients with IBS had abnormal tests compared with controls, and second, that oral neomycin normalized these results and reduced IBS symptoms [32]. Based on these data, the authors postulated that patients presented small bowel bacterial overgrowth, a conclusion that has been challenged by others [33].

The characteristics of colonic flora vary considerably among individuals [34], its composition apparently determined by early environmental conditions, with possibly also an adaptive component to the alimentary habits later in life [35,36]. One study reported that total hydrogen excretion (breath plus anal), measured by indirect calorimetry, was increased in patients with IBS, and the authors concluded that patients harbored a hyperactive gas-producing colonic flora [37]. To note, in this latter study, hydrogen excretion was increased, but the total gas excreted, hydrogen plus methane, was not.

Whether gas production in patients with IBS is increased, it is important to take into account that such a mechanism alone would not explain bloating. Various studies have shown that most healthy subjects are able to propel and evacuate very large gas loads without perception of abdominal distension, and as discussed previously, even fermentation of colonic lactulose loads may be associated with increased flatulence but no bloating. Conversely, many patients with bloating do not acknowledge increased flatulence [21,38].

If it is not solely increased gas production what produces bloating in most complainers, could it be gas maldistribution and focal accumulation? Various studies have shown that the volume of intraluminal gas is about 100 to 200 mL [39–42]. Considering the capacity of the entire GI tract, this is a relatively small volume, which underscores the complexity of the processes that determine the balance between gas input and gas output [34]. In people, the stomach invariably contains a small amount of gas (about 20 mL), and it is not known whether this gastric bubble accomplishes a physiological function or not. Air is introduced in the stomach by swallowing and is either eliminated by belching or emptied into the intestine. In the upper gut, neutralization of acids and alkalis produce large volumes of carbon dioxide [43], which because of its high diffussibility, is cleared rapidly from the gut into the bloodstream. Food residues arriving into the colon are fermented

by colonic flora-releasing gas, and the amount of gas produced depends on the pools of gas producing and gas-consuming micro-organism present in the lumen. Propulsion and transit of intraluminal gas determine the times for diffusion into the blood and for bacterial consumption. Hence, the rate of gas transit is a critical factor that influences the volume and composition of gas in the different regions of the gut [44].

The authors have measured intestinal gas transit and tolerance in their laboratory using a gas challenge test. Exogenous gas is infused continuously into the intestine, and gas evacuation, abdominal girth, and perception are measured simultaneously. The gas infused consists of a mixture of gases in venous proportions to minimize absorption. Using this technique, it has been shown that most healthy subjects propulse and evacuate as much gas as infused, up to 30 mL per minute, without discomfort [45]. However, the motor phenomena responsible for intestinal gas accommodation and propulsion are not known. Manometric studies detected no changes in phasic motor activity in response to slow infusion of gas in the small bowel [46]. Preliminary experiments using the barostat, however, suggest that gas infusion induces a tonic motor response: a contraction orad to the infusion site and a relaxation distal to the collection site [47]. These studies suggest that changes in tonic activity and capacitance of the gut may result in the displacement of large masses of luminal gas that offers low resistance to motion [48].

The methodology to measure gut motility and transit of solid/liquid chyme is established but has not helped so far in detecting consistent abnormalities in bloated individuals. Measurements of intestinal gas transit, however, have shown that patients with bloating have impaired intestinal handling of gas loads [29,42,49,50]. This subtle motor dysfunction, which may lead to impaired propulsion and abnormal distribution of intraluminal contents, may explain the bloating, particularly in these patients who also have gut hypersensitivity and increased perception. According to this hypothesis, minor motility disturbances that do not compromise function may become clinically relevant and produce symptoms in the presence of altered gut perception.

Among apparently healthy and asymptomatic individuals, there are some who deviate from the normal disposal of infused gas and retain gas during the gas challenge test. These asymptomatic gas retainers constitute about one in six of an unselected population [51]. In the presence of excess intraluminal gas, these apparently normal individuals would experience abdominal symptoms [52]. Indeed, it has been shown that different experimental models of increased colonic gas production, for instance by direct infusion of starch into the colon or by administration of an amylase inhibitor that causes malabsorption [53], produce abdominal symptoms in a relatively small proportion of healthy subjects [54]. Hence, a fraction of the healthy population with a subclinical dysfunction may develop bloating if certain circumstances concur. Others may dispose of excess gas as flatulence or simply derive no symptoms from colonic gas retention.

In contrast to healthy individuals, a large proportion of bloating patients meeting Rome II criteria for either IBS or functional bloating diagnoses have impaired transit and tolerance of intestinal gas when submitted to the gas challenge test [42,49,55]. These patients retain gas or experience abdominal discomfort in response to intestinal gas loads that are tolerated by most healthy individuals. Furthermore, the gas challenge test replicates their customary complaints.

The mechanism of gas retention in patients with IBS or functional bloating remains speculative. In theory, two different mechanisms could lead to intestinal gas pooling: increased resistance to gas flow and impaired intestinal propulsion. In healthy subjects, it has been shown that increased resistance to gas flow, modeled by self-restraint anal gas evacuation, results in gas retention associated both with distension and discomfort [56]. By contrast, impaired propulsion, modeled by glucagon-induced motor inhibition, produces abdominal distension, but largely painless gas retention [56]. In summary, abdominal distension depends on the volume of gas retained, but abdominal discomfort appears to derive from failure to propel gas, possibly because of uncoordinated intestinal motility rather than weak propulsion. Furthermore, abnormal distribution of gas with focal distension at various sites would increase perception by spatial summation phenomena [10].

In clinical practice, there are patients in whom the anus probably contributes to gas retention. Experimentally, this assertion is supported by the observation that in healthy subjects, voluntary anal contraction effectively leads to gas retention [56]. In most patients with bloating, however, retention of exogenous gas loads not depend not on anal function, but on intestinal motor disturbances, because retention occurs both when gas is collected by an external cannula, and when the anus is by-passed by an intrarectal collection device [57].

Under physiological conditions, gas transit is tuned by a series of reflexes acting at various sites of the GI tract [47,58], which normally interact to produce a net final effect. For instance, mild rectal distension has been shown to accelerate gas transit, whereas intestinal lipids have an inhibitory effect. Some evidence for disturbed regulation in patients with bloating has been gathered. It has been shown that the slowing effect of lipids is upregulated in such patients [49], whereas the prokinetic effect of distension is impaired markedly [59]. When the gas challenge test was applied in conjunction with intraluminal lipid infusion IBS/bloated patients could be differentiated clearly from healthy subjects. Patients retained large volumes of gas or became symptomatic, indicating that gas propulsion was ineffective or abnormally perceived to the point of becoming uncomfortable [49]. Moreover, using the gas challenge test, it was shown that retention of gas loads in patients with IBS and functional bloating was cleared effectively by parenteral neostigmine administration. The fact that this powerful intestinal prokinetic agent reduced gas retention and improved abdominal

distension and symptom perception [42] suggests that abnormal gas transit or perception of intestinal gas was responsible for the abdominal symptoms.

Scintigraphic studies using gas labeled with Xenon-133 have been applied to measure gas transit through different gut compartments. In healthy individuals, small intestinal transit time is similar to colonic transit time. These observations indicate that the speed of intestinal gas clearance is determined equally by the passage time through the small intestinal and colonic compartments. This behavior of intestinal gas is quite different from that of solid and liquid chyme. Segmental transit studies using the scintigraphic technique in patients with bloating showed that delayed gas clearance in patients is caused by impaired small intestinal propulsion, whereas colonic transit is normal [60]. Furthermore, when gas was infused directly at different levels of the gut by means of an intraluminal catheter, patients retained gas when infused into the jejunum, but not when infused into the ileum or cecum [60].

The hypothesis that abdominal bloating is caused intestinal gas intolerance is attractive. Other possibilities, however, must be contemplated. For instance, individuals with increased gas production who are unable to evacuate gas because of anal incoordination and functional outlet obstruction may retain gas in the colon and eventually become symptomatic, and the same would apply to individuals who retrain gas evacuation because of social constrictions. Furthermore, functional dyspepsia frequently is associated to IBS, and in these patients postprandial bloating may originate in the stomach rather than in the intestine [7,8]. These patients exhibit impaired meal accommodation of the stomach and increased gastric perception [8]. Thus, increased tension of the hypersensitive gastric wall, but not intestinal gas, may be the cause of dyspeptic bloating.

The potential role of abdominal muscular activity

The abdominal wall plays a key role in bloating. Visible abdominal distension involves a deformation of the anterior abdominal wall. Bloating as a subjective sensation could arise not from intra-abdominal organs, but from the abdominal wall itself because of increased tension or elongation of the abdominal muscles and other support structures. Indeed, the sensation of bloating could, at least theoretically, derive from a wall tension increment without a net elongation of girth, that is, even in the absence of true abdominal distension. There are several conditions that should be considered.

The first issue relates to whether patients with bloating have real abdominal distension and girth increment. For one, about 25% of patients admit the subjective nature of their problem and are aware that it is not associated to objective distension [61]. Still, most claim that their abdomen becomes swollen, and they need to unfasten their clothes. Even in these

cases, however, it is not entirely clear whether the claim of the patients is real. Some studies have measured girth changes in relation to bloating, and the results indicate that overall abdominal distension can be objectivated. Three independent studies used tape measures. One study compared two populations of patients, those who claimed that they were visibly distended and those who did not, and given the variability of girth in the normal population, not surprisingly no significant differences were found [62]. Two other studies measured intraindividual girth variations, however, and were able to show that girth increased during the day [63] and during episodes of abdominal distension [3]. More objective methods corroborated these results: CT imaging detected an increment in the anterior–posterior axis of the abdomen during the day [64], and preliminary studies with ambulatory inductance pletismography have shown that patients with IBS develop greater girth increment during the day in relation to bloating, particularly the constipation-predominant group [65].

By which mechanism does girth increase? Accommodation of intra-abdominal volume increments involves an adaptation with forward expansion of the anterior abdominal wall. Experimental studies have shown that the degree of distension depends on the intra-abdominal volume increment, and this was shown in healthy subjects and in patients with bloating using different models of intestinal gas retention [47,57]. Is the abdominal wall response the same in patients as in healthy subjects, however? A dystonic abdominal wall could fail to support adequately intra-abdominal contents and make the patient feel bloated, particularly in the erect position. One study reported weaker abdominal muscles in patients with bloating than in healthy controls [3]. Another study, however, did not found differences in abdominal electromyographic activity between IBS patients with bloating and controls. Specifically, this study showed that abdominal activity is higher in the upright position than in supine, and the response was similar in patients and controls [66]. These results were replicated recently in the authors' laboratory using a multiple electromyographic recording of individual muscle groups [67]. Using this method, the authors were able to demonstrate a dystonic response of the abdominal wall to intra-abdominal volume increments in patients with bloating. In healthy subjects in the upright position, the authors investigated the abdominal wall response to intra-abdominal volume increments. Intestinal gas retention, modeled by rectal gas infusion during anal blockade, increased abdominal electromyographic activity, conceivably reflecting and increment in tone, which likely is mediated by means of somatovisceral reflexes [68]. Patients with bloating exhibited an abnormal response. The same intra-abdominal volume increments induced an impaired contraction of the abdominal muscles, and the deficit was greater at the level of the internal oblique, a muscle with postural activity, which exhibited a paradoxical relaxation. This anomalous muscular response was associated with objective abdominal distension and bloating sensation. These results would support the

contention that muscular dystony of the abdominal wall may contribute to abdominal distension and bloating in some patients.

Protrusion of the abdominal wall can be produced by a redistribution of abdominal contents without net increments in intra-abdominal volume, and this is probably the case at least in a subset of patients complaining of visible abdominal distension. Alvarez reported on a series of patients with very pronounced abdominal distension with rapid onset that resolved instantaneously by relaxation or anesthesia without gas evacuation. He postulated that this was an intestinal-type distension [69].

Summary

Abdominal bloating is a relevant, troublesome, and poorly understood clinical problem. Despite its clinical importance, bloating remains substantially ignored, without proper clinical classification, known pathophysiology, and effective treatment. It is not even clear to what extent the complaints of individual patients correlate with objective evidence of abdominal distension, and this uncertainly regarding the subjective or objective origin of the complaints further adds to confusion. This article proposed a framework for investigating bloating, considering key factors potentially involved in its pathophysiology: distorted sensation, physical abdominal expansion, and abdominal wall dystony. Some data indicate that patients complaining of bloating have impaired transit and tolerance of intestinal gas loads. The problem does not seem to be too much gas, however, but rather abnormal responses to gas. Furthermore, abnormal control of abdominal muscle activity in these patients may contribute to objective distension. Bloating, like many other abdominal symptoms, probably represents a heterogeneous condition produced by a combination of pathophysiological mechanisms that differ among individual patients, resulting in a polymorphic clinical presentation.

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Brain Responses to Visceral and Somatic Stimuli in Irritable Bowel Syndrome: a Central Nervous System Disorder?

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Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterized by visceral hypersensitivity throughout the GI tract [1]. Most studies, however, have found normal to decreased somatic perception [2–6]. The exception is a recent study demonstrating that patients with IBS had rectal hypersensitivity and somatic hypersensitivity to thermal stimuli applied to the foot and to a lesser extent to the hand [7]. There has been considerable debate on the localization of visceral hypersensitivity (eg, peripheral versus central) in IBS, but there is evidence to support predominant central mechanisms. In recent years, an appreciation for central nervous system (CNS) modulation of visceral and somatic stimuli has occurred, particularly with the growing number of functional neuroimaging studies. Recent applications of functional brain imaging techniques of positron emission tomography (PET) and functional MRI (fMRI) have begun to more directly address the role of specific central networks in normal and altered processing of visceral and somatic related input. This article reviews the findings from functional neuroimaging studies that have evaluated central processing of visceral and somatic stimuli in healthy individuals and also provides evidence for alterations of these central networks to visceral and somatic stimuli in IBS.

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Visceral and somatic pain perception in irritable bowel syndrome

Visceral perception

Enhanced perception of visceral stimuli has emerged as an important pathophysiologic mechanism in IBS. When abnormal motility failed to be the primary mechanism to explain the etiology of IBS, a series of studies demonstrated that patients with IBS perceive noxious and non-noxious sensations to natural stimuli (contractions) or balloon distension of the small intestine [3,8–10] and rectosigmoid colon [4,11–15] at pressures and volumes that were significantly lower than in healthy individuals. The mechanisms of visceral hypersensitivity are not understood completely, and many factors (ie, genetic, motility, inflammatory, and psychosocial factors and stress) have been proposed as contributing to alterations in enteric and afferent spinal neural function and in CNS modulation of this information, which in turn produces long-term sensitization of pathways involved in the transmission of visceral sensation.

Somatic perception

In contrast to the findings of visceral hypersensitivity, most somatic pain studies have demonstrated that patients with IBS do not exhibit generalized hypersensitivity to noxious somatic stimulation [2–6]. A recent study, however, found that patients with IBS had rectal hypersensitivity and somatic hypersensitivity to thermal stimuli applied to the foot and to a lesser extent to the hand [7].

Brain activation patterns to visceral and somatic stimuli

There is growing evidence for altered visceral sensory, affective, and motor responses found in IBS to be associated with detectable differences in regional cerebral blood flow (rCBF) using functional brain imaging. Assessment of altered perception of visceral afferent information from the digestive system generally has relied on measurements of subjective ratings of controlled visceral stimuli. Recent applications of functional brain imaging techniques of PET and fMRI have begun to more directly address the role of specific central networks in normal and altered processing of visceral and somatic-related input. Functional neuroimaging is a novel method of studying central processing and modulation of brain–gut interactions in functional bowel disorders. There have been inconsistencies in the data, however, that may be caused by several factors, including methodologic differences, small sample sizes, varying characteristics of the patient population, and lack of attention to functional neuroanatomy of brain regions such as the anterior cingulate cortex (ACC). Before discussing brain activation patterns to visceral and somatic stimuli in IBS patients, analogous findings in healthy individuals will be discussed.

Healthy individuals

In healthy subjects, the brain regions most consistently activated in visceral and somatic pain are the mid/anterior insula, subregions of the ACC, prefrontal cortex (PFC), thalamus, and in some cases pontine regions such as the dorsal pons and periaqueductal gray (PAG). Although many areas are similarly activated in response to visceral and somatic stimuli, there are also differences. Two studies compared cortical processing of nonpainful visceral (rectal) and somatic (anal) sensation [16–17]. Both studies found similar areas of cortical activation; however, anal distension was associated with a more superior activation of the primary somatosensory cortex (SI) and a lack of ACC activation in one study [16] and additional activation of the SI and motor cortex, supplementary motor area, and left cerebellum in the other [17].

Two other studies compared rCBF in healthy subjects in response to visceral distension and cutaneous heat. Strigo et al [18] found that similar brain regions were activated in response to noxious esophageal distension and cutaneous thermal stimulation applied to the upper chest. These stimuli were matched for intensity but not unpleasantness (rated as greater for the visceral than somatic stimulus). Greater activation, however, was observed in the anterior insula bilaterally and the left ventrolateral PFC in the somatic group. Greater activation was demonstrated in a relatively more rostral subregion of the ACC for esophageal distension and a more dorsal subregion for cutaneous stimulation. The second study by Dunckley et al [19] found that when visceral and somatic stimuli were matched for unpleasantness, relatively greater activation occurred in regions that encode spatial orientation (dorsolateral PFC and inferior parietal cortex) during somatic (left foot and lower back) stimulation and in regions that encode emotion/interoception (right anterior insula) during rectal distension. Interoception is the sensation of the physiological self. These studies suggest that visceral stimulation is more likely to recruit areas encoding affect and interoception, while somatic stimulation is more likely to be associated with greater activation in areas involved with spatial orientation and motor response.

Irritable bowel syndrome

Studies previously compared the relationship between the intensity of lower intestinal balloon distension and regional brain activation in healthy controls [16,20–21] and in patients with IBS [22–28]. In general, several regions that are part of a central pain processing circuitry (central pain matrix), previously described in somatic pain studies [29–30] and supported by neuroanatomical data [31] (in particular the insula and the dorsal aspects of the anterior cingulate cortex) consistently were found to be activated in response to rectosigmoid stimuli [32]. In addition, other regions (including thalamus, SI and secondary somatosensory cortex) and limbic/paralimbic

regions and structures belonging to a corticopontine pain modulation system were activated to variable degrees in different studies. Preliminary evidence suggests alterations in patients with IBS occur in the activation of regions concerned with attentional processes and response selection (dorsal ACC and anterior midcingulate cortex) and cortical regions concerned with emotional and autonomic responses to stimuli (ventromedial PFC, perigenual ACC, and infragenual cingulate cortex) and subcortical regions receiving cortical projections from the latter and afferent input from the viscera (hypothalamus, amygdala, dorsal pons) in response to actual or anticipated but undelivered colorectal distension. Some of these findings are consistent with exaggerated threat appraisal, enhanced anxiety responses and hypervigilance toward gastrointestinal sensations in IBS patients [26].

The dorsal subregion of the ACC is an area that consistently is activated to a greater degree in patients with IBS compared with controls [25–26,33]. This region is concerned with cognitive processing of sensory input, including attentional processes and response selection. Furthermore, dorsal ACC activation has been shown to correlate with the subjective unpleasantness of visceral [22] and somatic pain [34]. These observations suggest that patients with IBS may fail to use CNS downregulating mechanisms in response to incoming or anticipated visceral pain. Furthermore, they show altered activation or deactivation of brain areas involved in emotional or cognitive processing of visceral stimuli, ultimately resulting in the amplification of pain perception.

The clinical relevance of the altered activation of these brain regions is supported by the findings that normalization of these patterns by different pharmacological and nonpharmacological interventions of this pattern may be associated with a reduction in IBS symptoms. Alosetron is a selective 5-HT_3 antagonist that is effective in relieving abdominal pain or discomfort and urgency and normalizing bowel habits in female patients with diarrhea-predominant IBS (IBS-D) [35]. Until recently, it was assumed that alosetron mediated its effects by means of peripheral $5HT_3$ receptors on enteric neurons, but recent evidence suggests that it also decreases activity in frontal and limbic structures including the amygdala, infragenual cingulate cortex, and ventromedial PFC, which are associated with improvement in IBS symptoms and emotional ratings (Fig. 1) [36,37]. There is also a case report of a woman with severe IBS with psychological distress who had resolution of activations in the region of the anterior midcingulate cortex/dorsal ACC and SI following termination of an abusive relationship, resolution of IBS symptoms, and normalization of psychological symptom scores [38]. These findings support the clinically significant contribution of centrally mediated modulation of visceral pain in IBS.

In an fMRI study comparing healthy controls and IBS patients, Verne et al [39] assessed cortical processing of visceral and somatic stimuli (ie, distensions of the rectum) with 35 and 55 mmHg pulses and immersion of the right foot into a heated water bath at 35, 45, and 47°C, respectively. IBS

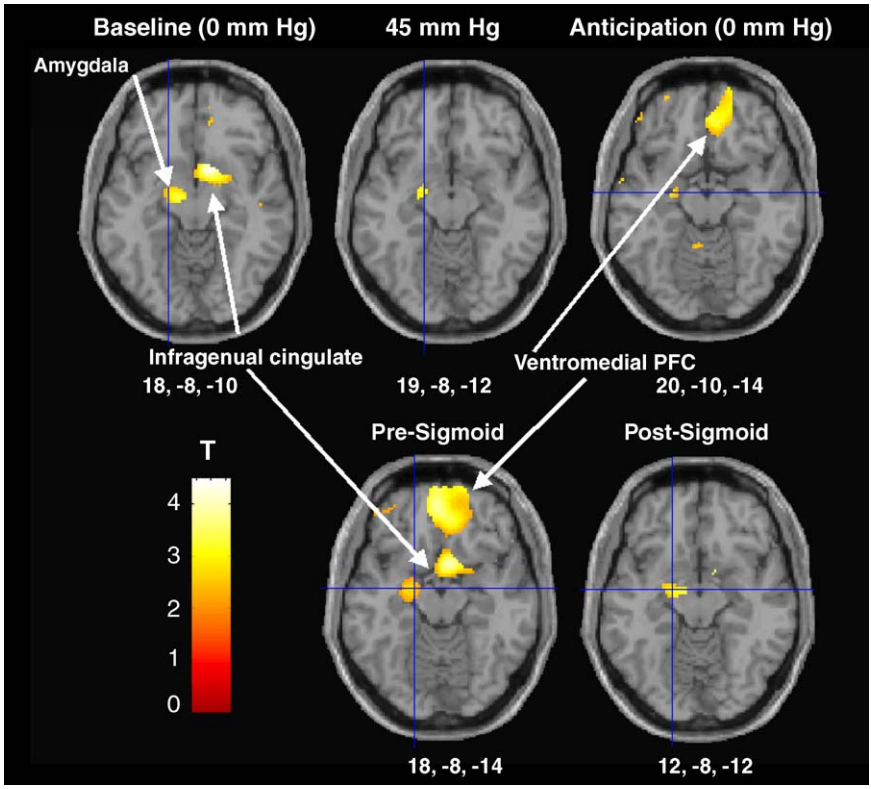

Fig. 1. Alosetron was associated with decreased rCBF to the amygdala. Effects are shown as statistical parametric maps (SPMs) with color-coded areas of significant ($p < 0.01$ uncorrected) rCBF decrease superimposed on a standard anatomical reference image from the Montreal Neurological Institute (the MNI brain). Crosshairs (coordinates labeled below) show amygdala deactivation in axial slices for all conditions. In all figures, left is right and right is left (radiological orientation).

patients rated the rectal and cutaneous stimuli as more intense and unpleasant than the control subjects. Despite rating the intensity of visceral and somatic stimuli similarly, the IBS patients reported significantly higher ratings of unpleasantness, fear, and anxiety for the rectal stimuli than the somatic stimuli. Compared with controls, IBS patients showed greater activation of the PFC, anterior and posterior cingulate cortices, thalamus, insula, and somatosensory cortex in response to the higher- level rectal and cutaneous stimulations. Rectal stimulation, however, was associated with activation of more areas within the PFC and thalamus. The authors concluded that these findings were more likely caused by increased ascending input to the brain rather than to altered cortical modulation of sensory information. The latter cannot be excluded completely, however, because significant activations occurred in the more rostral aspects of the

ACC and medial PFC that belong to an affective network that frequently is activated during anticipation of aversive events (rather than during the actual experience) [40] and during normal and pathological anxiety [41]. It is possible that patients with IBS show greater activation of limbic/paralimbic regions that may play a role in facilitation of perceptual responses.

There is growing evidence in the literature that IBS and fibromyalgia, the latter being a chronic condition characterized by somatic pain, are both biopsychosocial disorders that commonly overlap in the same individual [42]. These findings support the clinical impression that these two functional disorders share a common central pathophysiology [42–44]. A PET study compared rCBF in IBS and fibromyalgia patients with somatic and visceral pressure stimuli. Compared with IBS only patients, greater activation of the dorsal ACC subregion was found in patients with both IBS and fibromyalgia to a somatic stimulus compared with a visceral stimulus. Furthermore, this region was activated more greatly in IBS only patients in response to a visceral stimulus than a somatic stimulus compared with IBS patients with comorbid fibromyalgia (Fig. 2) [45]. The enhanced activation of this region in both IBS and fibromyalgia patients to visceral and somatic stimuli, respectively, suggests a similar central alteration of normal

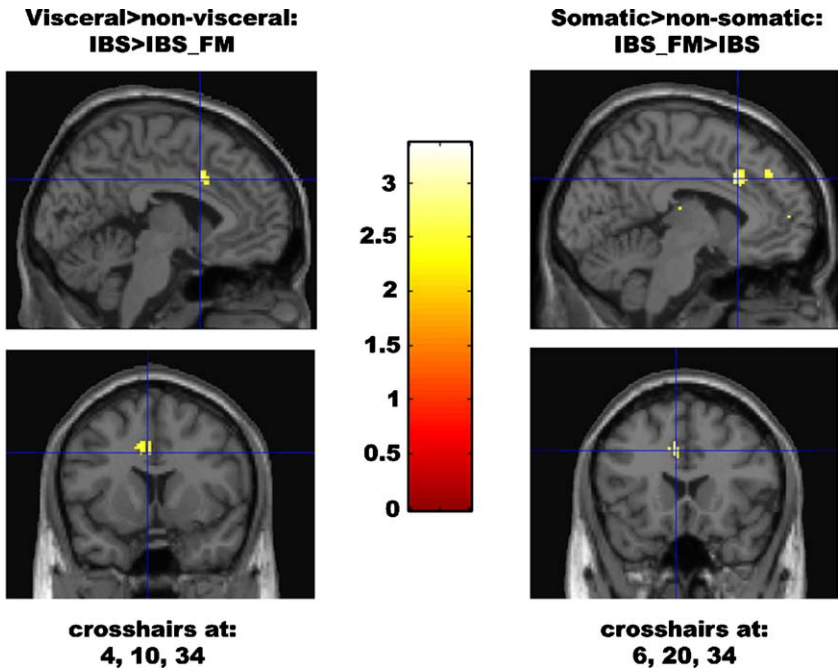

Fig. 2. Results for the interaction of type of stimulus (visceral, somatic, and clinical group (IBS and IBS + FM). There was greater activation of the dorsal ACC in IBS patients in response to visceral distension and in the IBS + FM patients in response to somatic pressure stimuli.

attentional attribution to specific afferent information from different body regions in IBS and fibromyalgia.

Summary

In healthy subjects, the brain regions most consistently activated in visceral and somatic pain are the key regions in the central pain matrix, including the mid/anterior insula, subregions of the ACC, PFC, thalamus, and in some cases, pontine regions such as the dorsal pons and PAG. Functional neuroimaging studies have demonstrated evidence of altered regional brain activation responses during visceral and somatic stimuli in IBS that have been associated with perceptual differences. Although perceptual studies have shown increased sensitivity to rectosigmoid distension in IBS, most somatic pain studies have demonstrated normal or decreased sensitivity compared with controls; however, a recent study showed increased sensitivity to thermal heat. Altered brain responses in IBS, particularly to visceral stimuli, include activation of regions concerned with attentional processes and response selection, corticolimbic regions concerned with emotional and autonomic responses to stimuli, and subcortical regions receiving cortical projections from the latter and afferent input from the soma and viscera. Altered activations of these regions also may be present in the absence of a noxious visceral stimulus. Changes in rCBF of some of these regions have been associated with treatment response in IBS. With regard to differences in cortical processing of visceral versus somatic stimuli in IBS, there have been only two studies. Greater activations of the dorsal ACC, thalamus, and PFC have been shown with visceral stimuli compared with somatic stimuli in IBS. A plausible hypothesis for the observations from brain imaging studies is that IBS patients demonstrate a compromised activation of pain inhibition circuits including those of the cortico-pontine circuit but increased activation of limbic and paralimbic circuits that may be related to pain facilitation.

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Psychiatric and Psychological Dysfunction in Irritable Bowel Syndrome and the Role of Psychological Treatments

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The understanding of irritable bowel syndrome (IBS) has evolved over the last 30 years from a simple and reductionistic biomedical view to a primarily physiological or motility-focused paradigm to the current dominant conceptualization that casts IBS as a complex multiply determined syndrome [1,2]. The present consensus is that IBS involves altered gut reactivity, altered pain perception, and brain–gut dysregulation [3]. Adding to this complexity is the fact that several factors, including biochemical, neurological, psychological, and social variables, can influence each of the domains of malfunctioning that contribute to IBS and thereby modulate the status of the disease and the patient's experience of illness. It is furthermore increasingly evident that no single factor is necessary to cause IBS and that multiple etiological variables may contribute to the disorder in a single patient.

Many psychological and social variables have been recognized over the years as significant factors in IBS predisposition, precipitation, and perpetuation. Although these factors are recognized as important by most gastroenterologists, they often are not evaluated effectively or addressed in IBS treatment. Many physicians continue to apply a narrower biomedical approach to IBS management, thereby only working with a part of the biopsychosocial equation that explains IBS. This is likely to contribute to the perception by many gastrointestinal (GI) doctors that as a group, patients with IBS are more frustrating and difficult to treat than other patients [4].

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Recognizing and addressing the psychosocial factors that amplify and perpetuate the disorder are important for enhancing clinical outcomes and well-being of many patients with IBS. By doing so, the physician sometimes can turn psychosocial stumbling blocks into stepping stones, achieving progress where the biomedical approach has hit a stonewall. This article reviews the role of adverse emotional and social factors in IBS and the ways in which the gastroenterologist can address such problems efficiently and effectively.

The epidemiology of adverse psychosocial factors in irritable bowel syndrome

Psychiatric disorders

More than 20 studies have examined the presence of psychiatric disorders in patients with IBS. Almost all of these studies have been conducted on samples of patients seeking medical care, mostly in tertiary care settings. The findings demonstrate that the presence of one or more Axis I psychiatric diagnosis is so common in clinical IBS patients that it might be considered to be a typical characteristic. According to recent systematic reviews of this literature [5,6], estimates of the proportion of patients who meet criteria for any Axis I psychiatric diagnosis have ranged from 40% to 94%, with several studies crowding on the upper end of that range. Patients with IBS generally have been found to have significantly higher psychiatric comorbidity rates in these studies than comparison groups of general medical patients or patients with organic GI disorders such as inflammatory bowel disease (IBD). The most frequent psychiatric disorders in clinical IBS patients are the same as the ones most prevalent in the general population. Depression is invariably the most common condition in studies of IBS patient samples, followed by anxiety and somatization disorders [5].

It must be noted that the empirical literature in this domain has several limitations that warrant caution in making generalizations and may inflate the psychiatric picture of IBS unfairly. Most of the studies have been small and have been conducted on tertiary care patients who are likely to be more distressed than other patients. Some of the studies have used subjects who specifically are seeking participation in treatment studies. Many studies have lacked adequate comparisons to other medical patients or other GI patients needed to determine whether high psychiatric rates are unique to IBS in the setting. A large and comprehensive study by Whitehead et al [7] in a health maintenance organization (HMO) sample, however, recently used methodology that avoids most of these problems. The investigators matched 3153 IBS patients in the electronic records of a large HMO to 3153 individuals without GI diagnoses and 571 IBD patients in the same HMO and examined psychiatric diagnoses on record for all of these patients. The

findings largely confirmed the psychiatric picture seen in previous work. IBS patients were significantly more likely than both comparison groups to have one or more psychiatric diagnosis in their HMO record. They had higher rates of 13 out of the 20 psychiatric diagnoses sampled in the study. At least one psychiatric diagnosis was documented for 51.2% of IBS patients compared with 34.7% in IBD and 29.1% of the controls. The three most common psychiatric diagnoses in IBS were depression (31.4% in IBS versus 21.4% in IBD and 17.5% in controls), stress reaction (17.6% in IBS versus 9.5% in IBD and 7.8% in controls) and anxiety (15.8% in IBS, 7.8% in IBD, and 6.4% in controls).

In summary, half or more of IBS patients in both GI clinics and other health care settings commonly have psychiatric comorbidity, most typically depression, stress problems, or anxiety, and these rates are substantially higher than for other medical patients in the same clinics.

The rates of psychiatric problems in IBS health care consulters are strikingly higher than the rates seen in general community samples of individuals with IBS, which do not always show elevated comorbidity. For example, Talley et al [8] compared a community sample of young adults in New Zealand with IBS to non-GI controls and found no significant differences in psychiatric history or current diagnosable psychiatric symptomatology. Other studies such as a large epidemiologic study by Lydiard et al [9], however, that found higher rates of panic disorder in people with bowel symptoms, suggest that increased psychiatric comorbidity may not be limited to those IBS patients who consult doctors.

Stressful and traumatic life events

In the last 15 years, several studies have documented an unusually high rate of sexual abuse history in patients with functional GI disorders. The first of these studies [10,11] assessed sexual and physical abuse history by means of a self-report questionnaire in 206 consecutive female patients visiting a gastroenterology practice in North Carolina. In the overall sample, 44% reported sexual or physical abuse either in childhood or adulthood. The sexual abuse rates were significantly higher for women presenting with functional GI disorders (53.3%) than for those with organic illness (37.3%). Rates of physical abuse were overall substantially lower than for sexual abuse, but showed an even sharper contrast between functional and organic GI patients (14.3% versus 1.6%). Later work by this group indicated that the difference in abuse frequency between the functional and organic diagnoses was explained primarily by higher frequencies of more severe abuse like rape and life-threatening physical abuse. Furthermore, the presence of abuse, independent of diagnosis, was found to be associated with significantly poorer health outcomes in terms of pain scores, days in bed, psychological distress, health care use including number of surgeries, and reduced quality of life [12]. Similar

observations of an association of functional GI disorders with high rates of abuse since have been made repeatedly in patients with GI problems in other clinic samples [13–16] and in a community sample [17]. One study [14] furthermore has found that sexual abuse history is more common among patients with lower GI rather than upper GI functional symptoms. Based on these data, recommendations have been made for clinicians to elicit a history of abuse, and if present, to determine if referral is needed [18].

Stressful life events other than abuse, such as break-up of an intimate relationship and other events viewed as threatening, more often precede the onset of IBS than organic GI illness [19,20], suggesting a predisposing or precipitating influence. Additionally, patients with the disorder typically report a higher density of recent stressful life events of high emotional impact on questionnaires compared with control subjects [21,22].

Maladaptive personal characteristics: neuroticism, dysfunctional coping and emotional distress

Several studies [21–26] have indicated that patients with IBS have elevated levels of neuroticism, which is a stable personality trait characterized by distress-proneness and negative bias in thinking. Catastrophizing is also a dysfunctional cognitive trait that repeatedly has been found to be elevated in patients with IBS and to be associated prospectively with poor health outcome [25,26]. These two aspects of cognitive bias are likely to mediate the heightened distress and psychiatric symptoms seen among IBS patients. High neuroticism causes individuals to identify more life experiences as personally threatening to them, and catastrophizing contributes to a morbid sense of pessimism and helplessness to affect a change.

Emotional distress is a subjective experience that may occur regardless of the presence of psychiatric illness or stressful life events. It can be measured by symptom questionnaires that quantify the frequency and intensity of negative emotions such as anxiety, worry, sadness, or anger experienced in a given time period, or alternatively by just asking subjects to rate their subjective feeling of stress. Both IBS patients and nonpatients who have IBS have elevated psychological distress levels compared with controls [27–30]. Interestingly, two studies [30,31] found that women with IBS reported a greater intensity of stress than controls even though the groups did not differ in the amount of stressful life events they experienced, suggesting that women with IBS amplify the negative intensity of life events.

Somatization and extraintestinal symptoms

Somatization is a concept that has been construed differently over the years. Studies on psychiatric comorbidity in IBS have found between

a quarter and a third of IBS patients to meet criteria for somatization disorder [5], which is much higher than in the normal population.

Traditionally, somatization has been viewed as a pathological psychiatric process that may have genetic determinants. In its most florid form, somatization presents itself as somatization disorder, a serious condition that involves multiple symptoms with little or no biological contribution, and which involve several organ systems over time. Several of other more limited somatoform disorders such as functional abdominal pain [32] and other painful conditions are also recognized, however, and in total, these are thought to be expressed because of a transduction of psychological distress into physical and behavioral expression. More recent studies using brain imaging suggest that the tendency to report visceral and somatic symptoms may relate to amplification of incoming non-noxious, or even regulatory afferent signals to emotional pain centers, and this amplification is enhanced by psychological stress [33–36].

Another way to conceptualize somatization is to view it as a psychological or behavioral trait, seen as the propensity to experience and report somatic symptoms, to misattribute them to disease, and to seek medical attention for them [37]. This trait can be assessed by using questionnaires that sample a wide range of commonplace body symptoms. Several such studies have reported excess somatization tendency in patients with IBS [38–40]. Non-GI symptoms such as musculoskeletal complaints, urinary symptoms, sexual symptoms, headaches, and constant fatigue typically are found at higher rates in IBS patients than in controls.

Illness behavior

Illness behavior refers to a person's verbal and behavioral response to physical sensations and symptoms. This response is abnormal when it is maladaptive, and this can occur when there is a less than expected and excessive response. For example, ignoring severe pain during acute myocardial infarction represents a maladaptive illness behavior that can be deadly, the appropriate behavior being the seeking of help. At the other extreme, the repeated seeking of medical care for inconsequential symptoms, often already evaluated, can increase health risk because of iatrogenic effects of multiple unnecessary tests and treatments. Empirical evidence suggests that IBS patients tend to have a lower than normal threshold for experiencing illnesses as distressing and acting in response to them by health care seeking. For example, individuals with IBS were more likely than those with peptic ulcer disease and healthy controls to report in a community telephone survey [41] that they interpret cold and flu symptoms as serious and that they visit doctors for such common problems. Another indication of maladaptive illness behavior in IBS is the finding that female IBS patients who have infant children seek medical care for their ailments significantly more often than other mothers [42].

The impact of adverse psychosocial factors on morbidity, health care use and treatment response

Psychosocial variables have been implicated by research findings as modulators of all aspects of the course, status, and consequences of IBS. Maladjustment in the psychosocial domain can amplify IBS severity, undermine treatment efforts, and contribute to increased health care use. Additionally, several psychosocial variables appear to predispose individuals to develop IBS.

Increased health care use and costs

Drossman et al [43] found that patients with IBS make three times the number of non-GI health care visits compared with control subjects. Levy et al [44] similarly reported that the average IBS patient in an HMO makes twice as many visits as other HMO subscribers. Seventy-eight percent of this excess use is for non-GI reasons, and very little of it is for psychiatric conditions. Furthermore, health care users with IBS recall greater attention to their illnesses as children with more frequent physician visits than persons with IBS who have not seen a physician [45]. These findings suggest that certain psychosocial factors play a role in mediating the high use of general medical care by IBS patients. It is unclear, however, to what degree this reflects lower threshold for consulting medical professionals because of abnormal illness behavior, amplification of physical symptoms, or psychological distress, respectively, but most likely the excess health care use results from a combination of these factors. For example, a German study by Herschbach et al [46] found that symptoms of depression and somatization were among the strongest correlates of increased number of doctor visits, and Koloski et al [29] reported that anxiety and worry about abdominal pain predicted frequent health care visits among IBS patients in a community sample. Additionally, a community survey by Talley et al [17] and a clinical population study [12] showed that IBS sufferers with abuse history are more likely to consult physicians for their bowel symptoms.

The same psychosocial factors that cause high health care use by IBS patients (but perhaps especially somatization and abuse history, which have been associated with excess surgeries in non-GI research) are likely to explain why IBS patients have higher rates of many different types of non-GI surgical procedures compared with other medical patients [12,47,48].

It should be noted that the relationship between high health care use and psychosocial variables is not unique to IBS. Such associations are seen in medical patient populations in general [49,50], but they may be more significant in IBS because of the unusual preponderance of adverse psychosocial factors in the disorder.

Impact on symptom severity

Most of the adverse psychosocial factors have been found to be related to symptom severity in IBS. Detailed analyses of changes in symptoms and life experiences of IBS patients over time demonstrate that increases in stressful life events are associated with greater bowel symptoms [21,30]. Higher subjective scores of emotional distress in patients with IBS also are associated with more intense and more persistent IBS symptoms [29,51]. A history of sexual abuse increases the probability of IBS being severe quite dramatically. IBS patients with abuse history have 65% greater pain scores and three times more time spent in bed because of illness [52]. Catastrophizing has a measurable amplifying impact on abdominal pain in patients with IBS [53,54]. And to complete the picture, Drossman et al reported that compared with patients with moderate illness, a sample of patients with severe functional bowel disease had greater pain scores, depression, psychological distress, and poorer coping strategies [55]. Notably there was no difference between groups in visceral sensation thresholds, suggesting the strong central influence on symptom severity.

Impact on treatment response

In their large multi-center treatment trial for functional bowel disorders, Drossman et al found that in contrast with other patients in the study, those who were depressed did not improve from psychological treatment or antidepressant treatment. Other studies have found psychiatric comorbidity to be a negative prognostic indicator for psychological treatment of IBS [56,57].

Impact on vulnerability to irritable bowel syndrome

The observation that several negative psychosocial factors that individuals generally carry with them from childhood are seen commonly in IBS strongly suggests that these factors make people vulnerable to develop the disorder or to perceive the symptoms as severe enough to seek health care, even though it is difficult to demonstrate a linear causation. The case for this assumption is strongest for neuroticism and childhood sexual abuse, respectively. Neuroticism is a partly genetically determined major personality trait that is fairly stable in individuals from early childhood (it is about the most stable of the so-called big five human personality dimensions). High neuroticism seen in patients with IBS is therefore likely to have been a part of their basic personality long before their first symptoms of the disorder. Neuroticism is also a predisposing factor in depression and anxiety [58], and constitutional neuroticism may help to explain the high rates of affective disorders in patients with IBS. It is unclear how or why neuroticism translates into vulnerability to develop chronic GI symptoms, but the work of Gwee et al [59,60] showing that individuals high on neuroticism (and

those high on anxiety, which may be related) are more likely to develop chronic IBS-type symptoms after an acute GI infection supports its role as a predisposing factor in postinfectious IBS.

The well-documented excess prevalence of abuse history in IBS, and especially childhood sexual abuse, indicates that some consequences of abuse increase the vulnerability to experiencing a greater severity of symptoms or increased illness behaviors with IBS. It now seems clear that visceral sensitivity does not play a role in the link between IBS and abuse history [61,62], and it may relate to increased central amplification of the visceral signals [34,63]. The heightened somatization and depression that characterize both abuse survivors and IBS patients, however, may provide a causal bridge between the two. Previous studies have shown that the effect of abuse on outcome appears to be mediated by increased somatic symptoms and psychosocial distress [64]. Further work is needed, however, to elucidate the nature of this connection.

A third psychosocial variable associated with IBS that the evidence suggests often antecedes IBS is reinforcement of illness behaviors in childhood. Studies have indicated that a history of modeling and reinforcement of the sick role and increased attention to illness in childhood [45,65,66] are unusually common among IBS patients, fostering greater attention to illness and health care-seeking behavior that persists later in life.

The integration of psychosocial factors in the biopsychosocial model of irritable bowel syndrome

An array of psychosocial variables has been identified that can have a deleterious impact on the clinical expression of IBS. Many individuals also possess adaptive psychosocial traits such as good coping resources or social support that can counter or neutralize the potential negative influences of disturbed bowel physiology such as increased motility or visceral hypersensitivity. Furthermore, individual physiological and genetic differences may make some people less vulnerable to the disturbance of GI functioning by psychosocial influences. The outcome for each patient, whether health care visits, quality of life impairment, or pain intensity, is a result of the interacting effects of intestinal physiology; the enteric and central nervous systems; and perceptual, cognitive, emotional, and behavioral aspects of the patient. This complex relationship is summarized in Fig. 1.

It also should be noted that there is a reciprocity of influence between symptoms and clinical outcome, such that an adverse clinical outcome (eg, disability or narcotic use for pain) can feed back on the brain–gut system, leading to adverse bowel physiological and central effects, thus creating a vicious cycle.

It is important to recognize that not all patients with have prominent psychosocial difficulties. The relationship between bowel physiology and the

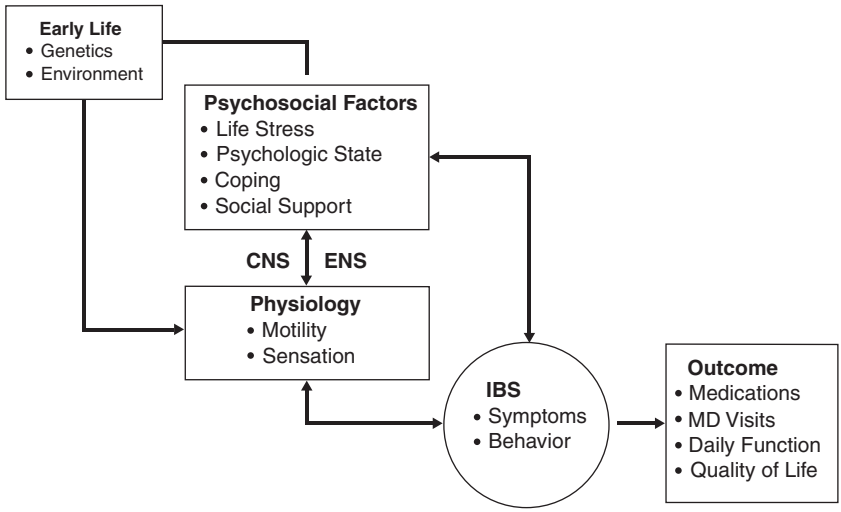

Fig. 1. Conceptual model of irritable bowel syndrome.

psychosocial milieu exists on a continuum. Most people with IBS have milder illness with adaptive psychosocial features, and only a small percent have maladaptive psychosocial difficulties that amplify the illness experience and behavior. Evidence is accumulating to support the heterogeneity hypothesis of IBS [5], which is fully consistent with a biopsychosocial understanding of the disorder [67]. In this view, psychosocial factors may weigh heavily for some patients, whereas other patients with the same disorder and largely the same symptoms may have predominant physiological influences with less evidence of deleterious psychosocial factors. For example, a recent cluster analysis by Guthrie et al [68] on a sample of 107 patients, examining how a variety of characteristics grouped together in the patients, found indications of three distinct patient groups. One group (the psychosocial group) was characterized by high rates of psychiatric morbidity; low pain thresholds; and high rates of doctor visits, interpersonal problems, and sexual abuse. A second group had low pain thresholds but low sexual abuse rates and only moderate psychiatric morbidity. The third had high pain thresholds, constipation or alternating bowel habits, few doctor visits, and little sexual abuse. Similarly, Dunlop et al [69] found that a history of psychiatric diagnoses was only half as frequent in IBS of postinfectious etiology compared with nonpostinfectious IBS cases. The findings from both of these studies need to be replicated in larger samples, but they underscore that it is a subset of IBS patients who have prominent psychosocial features in their broad illness picture. Those are the patients who are likely to respond poorly to standard medical treatment and to have the most severe and disabling symptoms unless the psychosocial factors can be addressed effectively.

Successfully addressing adverse psychosocial factors in irritable bowel syndrome

Gastroenterologists have three principal ways to neutralize the deleterious effect of adverse psychosocial factors on morbidity and chronicity in IBS. These are the therapeutic doctor–patient relationship, psychotropic medications, and referrals for psychological treatment. Of these, the power of the first is the one most underestimated. This is unfortunate, for not only is it as potent as the other intervention methods, but it is also crucial for enabling the effective application of the other two interventions. Patients are far more likely to comply with treatment with psychotropic medications and to accept referrals for psychotherapy if this is done within the context of a good doctor–patient relationship. In the absence of biomedical tools that can address the symptom complex of IBS for most patients reliably, the therapeutic relationship is overall the single most important therapeutic tool for treating patients with IBS [70].

The therapeutic relationship

An effective therapeutic relationship is one that actively contributes to symptom reduction and the enhanced life functioning and well-being of the patient. Physicians can create an effective therapeutic relationship with a fair amount of reliability by attending to five key aspects of their interactions with patients.

Active listening

Adopting this interviewing style enables the physician to identify and address psychosocial contributing factors far more effectively than with typical medical interviewing. It can be accommodated in standard history-taking. Active listening is a facilitative, open-ended style that invites the patient to contribute at each turn not only basic objective facts but also his or her understanding, viewpoint, and the relevant psychosocial correlates of the medical topic at hand. This is done through open-ended questions such as ''can you tell me more about your symptoms?'' and ''what else?'' as well as facilitative comments, facial expressions, and pauses when relevant material is brought up. Important references to psychosocial problems often are presented by patients in the form of hints and incomplete tidbits, and picking up on these is a key skill. Often simple and nondirective questions like ''can you tell me more about that?'' at the right junctures quickly provide important details. Showing appropriate empathy (''That must have been hard for you''), interest in the patient's own perspective (What do you think could be making your symptoms worse now?), and expressing interest and curiosity in the perceived social and emotional effects of the bowel problem as perceived by the patient facilitate this type of interviewing and quickly foster good rapport.

Although this approach to interviewing might be perceived as likely to lead to unneeded information, this does not occur if the physician actively listens and maintains the narrative thread of the interview. In fact, the time spent in this manner yields higher quality information that can help in making management decisions. Active listening provides three important kinds of information about the patient that may not be gathered effectively through a more directive approach. It provides a comprehensive sense of the role of psychological and social factors in the patient's IBS condition and discovers unmet educational needs and patient concerns and fears about the disease. Chang and Drossman provide a detailed description of this interviewing technique and related skills of psychosocial interviewing specifically for IBS [70].

Education

Providing a thorough explanation of the disorder is perhaps even more important for IBS patients than for other GI patients because of the complexity and ambiguity of the disorder. IBS patients have unmet education needs more frequently than patients with other GI conditions. O'Sullivan et al [71] found that 77% of patients with IBS coming to a GI outpatient clinic needed more information about their condition. They also reported that the top two education needs related to cancer risk from IBS and diet.

Reassurance

Reassurance consists of bringing out into the open and responding to the patient's concerns and fears about the disease. The patient may have fears and worries that the physician does not anticipate. It is therefore important to elicit them through open-ended questions like "are there particular things that worry you about your IBS?" Even though some patient worries may seem unusual, they are important to them, and being able to voice them permits the physician to respond to them. Confident reassurance in regard to key disease-related concerns can go a long way to treat the disease-focused anxiety of the patient.

Setting appropriate expectations and goals

This applies to all central aspects of the patient's experience related to the disorder, including expectations regarding the normal course or variability in symptoms, adverse effects of medications, the appropriate and available working relationship between the doctor and the patient (eg, frequency of visits or phone calls), and events that do and do not need attention from the health care staff.

IBS is a chronic condition, and most patients will continue with symptoms for many years. Setting goals and expectations for the future that are unachievable will undermine the continued doctor–patient relationship and can lead to unnecessary return visits. Giving patients an accurate

estimate of the prognosis while instilling a sense of hope and physician availability can help improve the patient's perspective, and this has been associated with greater satisfaction in care and clinical outcome [72]. It helps to set reasonable targets so the patient can learn to better cope with symptoms, finding ways to keep the symptoms from interfering with life (for example, preventing bowel accidents or keeping abdominal pain from being incapacitating) and increasing well-being and quality of life.

Giving the patient a clear sense of dependable access to help if needed, but with clear guidelines for the types of situations and events that are cause for medical attention, can put him or her at ease and reduce the patient's need for visiting or contacting the health care provider.

Actively involving the patient

Patients with IBS can benefit in numerous ways if they can be allowed and be interested in taking on the role of a well-informed coinvestigator in their condition with the physician as a mentor, examining contributing factors and arriving collaboratively at the best treatment choices. When successful, this can enhance the patient's motivation to comply with treatment, foster a more positive doctor–patient relationship, and mobilize the coping resources of even the most chronically passive patients. It also can lead to new insights as the patient accepts the responsibility to bring observations to the table that otherwise would go unexamined. By turning a "heal me" stance into "help me to find ways to improve," IBS patients who have surrendered their sense of control to the unpredictable nature of their bowel disorder can regain motivation and sense of self-efficacy that over time can translate into less need for consulting health care providers.

With certain patients who are open to exploring the role of psychosocial influences to their condition, the gastroenterologist can try to implement key aspects of cognitive therapy. He or she can help the patient to reconceptualize the problem more realistically and in a healthy context, facilitate reducing catastrophizing and black-and-white thinking, and stimulate identification of new coping strategies and recognition of the relationship between life stress and symptom exacerbation. Such interventions can come informally in patient encounters and yet yield real therapeutic results.

Clinical impact of an effective therapeutic relationship

Studies indicate that when the central pillars of a good therapeutic relationship are in place, they are associated with enhanced patient satisfaction, better clinical outcome, and reduced health care visits. For example, in a study of the medical records from IBS patient visits, Owens et al found that eliciting on the first visit the patient's concerns, providing appropriate reassurance, doing an appropriate evaluation, providing continuity of care and other factors that enhanced physician–patient communication [73] were associated statistically with fewer subsequent

health care visits [74]. O'Sullivan et al [71] found that good patient education (as perceived by the patients) resulted in less health care use.

Not unimportantly, the physician's own satisfaction is also likely to increase when the essentials of the therapeutic relationship are implemented effectively [4]. Jackson et al [75] have demonstrated in a controlled study that incorporating such psychosocial interviewing tasks as eliciting the patient's worries and expectations actually reduces the physician's perceived difficulty of the encounter while at the same time enhancing the patient's satisfaction with care. They further found that taking the time to do this did not add to the cost of care or affect health care use. Routinely attending to the fundamentals of a solid therapeutic relationship is thus a win-win situation for the doctor and patient.

Psychotropic medications

Antidepressants have proven effective for abdominal pain and are recommended for moderate and severe IBS symptoms [76]. They typically are used in IBS management at low doses for their neuromodulary effects. The high prevalence of psychiatric illness in IBS, which afflicts half or more of the patients visiting the gastroenterologists office, makes management of psychiatric symptoms with psychotropic drugs appropriate at times, however. Treating comorbid psychiatric disorders such as major depression or anxiety disorders with antidepressants or anxiolytics can reduce the impairment associated with the bowel disorder greatly in some patients and enable them to use of their coping resources to adjust better to their health problem. It is believed that psychotropic medications like antidepressants have central and peripheral neuromodulatory effects [2,77].

Referrals for psychological treatment

The current American Gastroenterological Association medical position on IBS [76] states that psychological treatments should be initiated for patients with IBS under two conditions: when symptoms are severe enough to create significant impairment in health-related quality of life and when there are comorbid psychiatric conditions that interfere with adjustment to the illness. These two conditions require a different approach to referral, as the goals are different. In the first case, the goal is to improve the clinical picture of IBS, and in the second, to improve the mental health and life functioning of the patient regardless of detectable direct role of psychiatric illness in the IBS condition.

Most mental health professionals are trained to treat psychiatric illness and psychological and social maladjustment, and referral for treatment of psychiatric comorbidity therefore does not require much special consideration by the gastroenterologist. When the aim is to improve severe IBS through psychological treatment (rather than treating comorbid psychiatric

illness), however, some care must be taken in choosing the psychological treatment for which referral is made. Only a few specific approaches have adequate empirical support as being effective in improving the overall clinical picture of IBS. General mental health treatment is not necessarily likely to make any impact on IBS, especially if the patient does not have significant psychiatric symptoms.

Psychological treatments that are effective for irritable bowel syndrome

Several different psychological treatment approaches have been tested for IBS. Most of these have shown some initial promise in improving IBS in published studies. It must be kept in mind, however, that placebo response rates tend to be high among patients with IBS receiving any treatment. Additionally, because of the added cost, psychological treatment should be more effective than could be expected from a generic plausible treatment. There are four specific psychological therapies that have been tested adequately in controlled studies to indicate that they can be recommended for treatment of IBS.

Cognitive therapy

Cognitive (or cognitive–behavior) therapy is a semistructured form of psychotherapy where the therapist helps patients to correct biased and negative thought patterns that amplify physical symptoms and undermine effective life functioning and psychological well-being. This is done by increasing awareness of the association between stressors, thoughts, and symptoms; by examining and correcting irrational beliefs; by countering automatic negative thoughts; and by identifying and implementing more adaptive coping strategies to handle challenging life situations and deal with bowel symptoms. These cognitive interventions often are combined with behavioral interventions like encouraging patients to engage in activities that counter the disability associated with the bowel disorder. In IBS treatment, cognitive therapy is usually a course of 8 to 12 sessions [78].

Six controlled studies have been reported on cognitive or cognitive–behavior therapy for IBS. The largest and most methodologically sophisticated of these studies was conducted by Drossman et al [79,80]. They randomized 431 women with functional bowel disorders (most met Rome criteria for IBS) to a 12-week course of cognitive–behavior therapy or the same amount of education intervention (and simultaneously compared the effects of these interventions to the tricyclic antidepressant desipramine versus placebo capsules). Cognitive–behavior therapy resulted in treatment response rate that was almost twice as high (70% versus 37%) as seen in the education control group on a broad composite outcome index that included bowel symptoms, quality of life, and patient satisfaction with treatment. The

treatment response was not significantly different between desipramine and cognitive–behavior treatment.

Two cognitive therapy studies by Blanchard et al [81,82] also yielded very positive results for cognitive therapy. One of these [81] randomized 34 patients to 8 weeks of cognitive therapy, a self-help support group, or a waiting-list control group. Cognitive therapy patients had 66% reduction in the composite bowel symptom score after treatment, twice the reduction among control patients, and this improvement was maintained at 3-month follow-up. The second study by this group studied 20 patients and found that patients who received cognitive therapy had greater improvement in psychological and GI symptoms compared with a waiting-control group [81,82].

Three additional controlled trials of cognitive–behavior therapy for IBS have produced less impressive results. Two showed no differences between patients treated with cognitive–behavior therapy and standard medical care controls [83,84], and one found psychological improvement over control groups but no significant IBS symptom improvement [78].

In addition to these six controlled trials, cognitive therapy has been tested in additional controlled trials as a part of multi-modal packages where it has been combined with other treatments such as relaxation training and biofeedback. It also has been tested in uncontrolled studies. Many of these trials have shown positive treatment results.

Gut-directed hypnosis

Hypnosis treatment uses an altered mental state of heightened receptivity, problem-specific therapeutic imagery, and targeted verbal suggestions to achieve mental and physiological changes. In IBS therapy, this treatment is typically a course of 7 to 12 weekly or biweekly sessions. Each session consists of a hypnotic induction followed by trance-deepening instructions and imagery and hypnotic suggestions designed to produce overall physical relaxation, gut-specific relaxation, reduction in the perception of life threat, lessened attention to gut discomfort, and enhanced sense of control over symptoms.

Hypnosis for IBS has been tested in three small controlled trials and 12 uncontrolled studies. Whorwell et al [85] randomized 30 severe and refractory IBS patients to either seven individual sessions of hypnotherapy or seven sessions of individual psychotherapy combined with placebo pills. The control group showed a small but significant improvement in abdominal pain, distension and general well-being, but showed no change in constipation or diarrhea. In contrast, the hypnotherapy patients showed significantly greater improvement in all central IBS symptoms, including bowel activity symptoms. The other two randomized controlled studies [86,87] used symptom-monitoring waiting list members as controls, and both found hypnotherapy patients to improve substantially more in GI and

psychological symptoms compared with the waiting groups. Improvement was well-maintained at follow-up in both studies.

In addition to these controlled trials, recent published reports [88,89] on the long-term outcomes for more than 200 consecutive IBS patients treated with hypnosis in England have added substantially to the knowledge of the potential benefit from hypnosis for IBS. Seventy-one percent of patients responded to treatment. Among those responders, 81% fully maintained improvement at follow-up 1 to 5 years later, and many of the remaining 19% had experienced only modest relapse in symptoms. Treatment responders also used significantly less medication and had fewer health care visits long-term.

Psychodynamic therapy

This is a form of psychotherapy derived from psychoanalysis. It is a highly individualized conversational therapy that aims to help patients to gain insight into their own condition and resolve emotional and interpersonal conflicts that are thought to contribute to their symptoms.

Two early controlled trials showed this treatment to be effective for IBS. Svedlund et al [90] randomized 101 patients to psychodynamic therapy versus medical management alone. The psychodynamic group had significantly more reduction in physical symptoms, and the contrast was even more pronounced at 1-year follow-up. Guthrie et al [91] randomized 102 patients with refractory IBS symptoms to either eight sessions of psychodynamic interpersonal therapy or five sessions of supportive listening. The psychodynamic patients improved significantly more than the other group and remained improved at 1-year follow-up.

A more recent trial, the largest for this kind of therapy for IBS [92], randomized 257 patients to either eight-session psychodynamic interpersonal therapy, selective serotonin reuptake inhibitor antidepressant (paroxetine), or standard medical care. There was no significant therapeutic effect on symptoms for either psychotherapy or medication compared with standard care at the end of treatment or at follow-up. Both treatment groups, however, improved significantly in some aspects of quality of life, and the psychotherapy group had lessened health care costs compared with the other groups at follow-up.

Relaxation training

Relaxation training aims to help patients reduce their own physical tension and emotional distress through techniques such as progressive muscle relaxation, autogenic training, meditation, or biofeedback. It is a particularly suitable option for IBS patients who have a clear association of their symptoms with stress or anxiety. Relaxation training often is used as a component in other treatments, but it has been studied as the main or sole

therapeutic ingredient in three controlled studies. Two of these [93,94] demonstrated that IBS symptoms improved more compared with standard medical management groups, but the third [95] found no group difference. In the two positive trials, improvement was well-maintained at follow-up.

In short, most studies on each of four psychological treatment types have shown them to improve IBS. Perhaps most impressive about this body of research is the fact that many of the studies only have included subjects who already failed to improve in standard medical treatment, indicating that psychological treatments are often a way forward for treatment-refractory IBS patients. The research has demonstrated further that these therapies improve psychological well-being and quality of life of the patients in addition to reducing bowel symptoms, and that the therapeutic benefit, when achieved, generally can be expected to last for years.

Making a successful referral for psychological treatment

It has been estimated that half of patients referred for psychological or psychiatric treatment by primary care physicians never follow through and receive such treatment. Even though no comparable data are available for gastroenterology, it is likely that the picture is similar. Proper preparation of the patient is crucial for successful psychological referral. The patient must understand that the referral makes sense in the context of the IBS problem, that he or she is not being dumped, and that he or she will have continued access to care for the bowel symptoms. It is also important that the patient does not perceive the referral as an indication that the gastroenterologist thinks that the problem is all in the patient's head. If the referral is made for treatment of comorbid psychiatric illness, it should be explained to the patient that the purpose is to help to reduce the emotional burden associated with the disorder as a part of aiding the patient in feeling and functioning better. Discussing the referral in the context of discussing the patient's life stress, the emotional toll of the illness or coping difficulties, makes bringing a mental health provider into the treatment picture seem more relevant.

If the goal of the referral is to achieve improvement in IBS symptoms, explanation of the brain–gut relationship in IBS is in order. Discussion of the evidence that psychological treatments reduce abdominal pain, for example, can help the patient see the treatment as mind–body IBS treatment rather than a mental health treatment.

Additional considerations in deciding which patients to refer for psychological treatment should include the following:

- Psychological mindedness. Only patients who are willing to entertain the idea of a role for stress or psychosocial factors in their condition are likely to be accepting of referral.

- Motivation to actively participate in treatment. Psychological treatments require substantial work by patients and a commitment to a course of several visits.
- Local availability of effective treatments. Cognitive therapy is one of the most commonly used treatment methods in professional psychology, and relaxation training is also in wide use, so finding therapists to provide these services is generally not difficult. In regard to cognitive therapy, it is very helpful if the therapist is experienced in treating functional GI disorders, for the approach is specialized partly to the nature of the condition. Hypnosis treatment is not as widely available, but clinicians using that method can be found in almost every urban area. Extra caution needs to be exercised with hypnosis referrals, because the practice of hypnosis outside regulated health care professions is not restricted by law in many parts of the United States, so lay hypnotists also offer their services. Only licensed mental health professionals (eg, psychologists, clinical social workers, psychiatrists, and mental health nurses) should provide this service for IBS. As with cognitive therapy, it is desirable that the hypnotherapist is experienced in GI-specific treatment. Psychodynamic interpersonal therapy of the specific kind tested for IBS generally is not available in the United States.
- Insurance coverage or financial resources. Psychological treatment is generally reimbursable under the mental health portion of insurance plans. Some patients who do not have the required insurance coverage may want to pay out of pocket for the therapist fees. As the therapy course for IBS treatment is generally brief, the cost is within the means of many patients.

Summary

Psychosocial variables play a substantial role in the IBS condition of many patients. Evaluating and addressing adverse psychosocial factors is important to achieve satisfactory clinical outcomes with those patients. This can be achieved efficiently through psychosocial interviewing, establishing a solid therapeutic relationship, and judicious and tactful application of psychotropic medications and psychological treatments. Success in addressing psychosocial factors in clinical encounters benefits not only patients, but also the gastroenterologist through increased work satisfaction because of reduced difficulty and frustration in working with IBS patients.

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Genetics and Genotypes in Irritable Bowel Syndrome: Implications for Diagnosis and Treatment

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Irritable bowel syndrome (IBS) is a multifactorial disorder, and several pathophysiological mechanisms have been proposed, including altered bowel motility, visceral hypersensitivity, psychosocial factors, an imbalance in neurotransmitters, and infection [1]. Both intrafamilial learning and genetics could play important roles in the pathogenesis of IBS. Several studies have provided evidence for a genetic contribution to IBS [2–5]. There is no doubt that the environment influences the development of IBS, and several studies suggest that nurture is certainly important, as it influences the effect of nature [4]. Recently, it has been proposed that several genetic markers are associated with some aspects of IBS. This article discusses the genetic associations reported in IBS patients and critically appraises their potential role in diagnosis and treatment of IBS.

Genetics in irritable bowel syndrome

One form of investigation of the potential genetic component in functional gastrointestinal (GI) disorders has addressed familial aggregation and twin studies. These will be discussed separately.

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Twin studies

In 1998, Morris-Yates et al [3] published the first twin study of IBS; 686 same-sex twin pairs enrolled in the Australian Twin Registry were interviewed by carefully trained lay interviewers using a general symptom inventory. Of the 686 individual twins, 33 (4.8%) had one or more GI symptoms. Concordance for functional bowel disorders (FBD) was 33% for monozygotic twins versus 13% for dizygotic twins ($P < 0.05$). These results suggest that a substantial proportion of the propensity to develop FBD may be under genetic control. Levy et al [4] analyzed responses from a large US twin registry. This analysis was based on 10,699 respondents representing 6060 twin pairs. IBS was inferred if participants reported that they had IBS on a general medical history questionnaire; the subjects also were asked whether their parents had a diagnosis of IBS. Concordance rates for self-reported IBS diagnosis were 17% for monozygotic twins compared with 8% for dizygotic twins ($P < 0.05$), supporting a genetic contribution to development of IBS. The proportion of dizygotic twins with IBS whose mothers also were reported to have IBS, however, was greater than the proportion of dizygotic twins with IBS who had cotwins with IBS. This result implies that social learning has an equal or greater influence than genetic factors. Mohammed et al [6] reported a different result from another twin study involving 4480 unselected twin pairs who completed a validated questionnaire. IBS was defined on the basis of the Rome II criteria. Concordance rates were 16% for monozygotic and 17% for dizygotic twins.

Thus, the first two twin studies have shown there is an increased concordance of IBS in monozygotic versus dizygotic twins, supporting a genetic component in contrast to the latter. How can these data be reconciled? At this stage, it is difficult to conclude that there is a definite genetic component in IBS. These three twin studies had significant limitations. The first two studies used imprecise methods of defining IBS cases; moreover, most of the twins in all three studies were raised together, making it difficult to distinguish genetic from environmental influences.

Familial aggregation studies

Locke et al [2] performed a cross-sectional study and observed that patients who reported a family member with abdominal pain or bowel problems had a twofold increased risk of reporting symptoms of IBS. This risk may be attributable to genetic or common environmental factors, or both. The method used to appraise familial involvement was the subjects' reporting of family members' symptoms, however, and the validity of this method is not known. The same group [5] prospectively compared the prevalence of IBS between the relatives of patients with IBS and relatives of controls who were the index patients' spouses. A valid self-report bowel disease questionnaire (BDQ) was mailed to IBS patients and spouses. The

prevalence of IBS was 17% in patients' relatives versus 7% in spouses' relatives, and the calculated sex, age-adjusted odds ratio (OR) was 2.72 (95% confidence interval [CI], 1.18 to 6.26). Thus, these results suggest that there is either a genetic or intrafamilial component in IBS.

Increased concordance of IBS in monozygotic versus dizygotic twins and familial aggregation in IBS may support a genetic component and would provide the rationale to search for genetic causes. The authors have reviewed the data of the potential genetic markers investigated in IBS.

Genotypes in irritable bowel syndrome

Inflammation of the intestine, immunomodulatory factors, psychological factors, or derangements of the neural control of the gut may play important roles in the pathogenesis of IBS in some individuals. Studies have investigated genetic variations in the control of these putative mechanisms.

First, cytokines are involved in the regulation of immune and inflammatory responses, and the production of cytokines is under genetic control. The genetic polymorphism of the three cytokines, including interleukin (IL)-10, tumor necrosis factor α (TNF-α), and transforming growth factor (TGF)-β_1 have been investigated in patients with IBS [7,8]. Second, there is evidence of sympathetic adrenergic dysfunction in a subgroup of patients with IBS [9,10]. Third, other neuromodulators and translational mechanisms may play a role in IBS. Serotonin and norepinephrine modulate sensorimotor functions in the digestive tract, and α_2-adrenoreceptor [11], G-protein β_3 subunit [12], and serotonin transporter [11,13–15] polymorphisms also have been compared between patients with IBS and normal controls.

Genetic variation in the control of inflammation in irritable bowel syndrome

There is increasing evidence that a subset of IBS has an inflammatory component that may be persistent long after acute infectious gastroenteritis [16]. Cytokines are involved in the regulation of immune and inflammatory responses, and cytokine imbalances presumed to result from cytokine gene polymorphisms are associated with numerous nonimmunologic diseases [17]. TNF-α and interferon-γ are proinflammatory, while IL-10 and TGF-β1 have anti-inflammatory properties.

Gonsalkorale et al [7] studied 230 unselected patients with IBS and 450 healthy controls. An IL-10 polymorphism (-1082) is known to influence IL-10 production in lymphocytes. The G/G allele is associated with high production and the A/A allele with low production of IL-10. Patients with IBS had significantly reduced frequencies of the high producer genotype for IL-10 compared with controls (21% versus 32%). This result suggests that at least some patients with IBS may be genetically predisposed to produce

lower amounts of the anti-inflammatory cytokine IL-10. In the same study, TGF-β_1 genotypes were examined in 134 IBS patients and 127 controls. Allele and genotype frequencies for TGF-β_1 were not different between patients with IBS and controls, both at codon 10 and at codon 25. The same IL-10 single nucleotide polymorphism (SNP) at position G-1082A and a separate polymorphism at C-819T were studied in a separate cohort of 111 IBS patients and 162 healthy controls in a recent study also from Northern Europe [8]. Both IL-10 SNP genotypes were distributed similarly between patients and controls in the Dutch study, in contrast to the prior study from northern England. Thus, the SNPs related to IL-10 and TNF-α are contradictory in IBS patients from the Netherlands and England.

Variation in potential genetic control of neurotransmission in irritable bowel syndrome

Serotonin transporter polymorphism

What is serotonin transporter (SERT)? 5-HT is secreted in copious amounts from gut enteroendocrine cells and serves as a critical messenger for GI fluid secretion and gut motility [18,19]. There are several classes of serotonergic receptors, differentiated on the basis of structure, molecular mechanism, and function [20]. In contrast to the diversity of 5-HT receptors, only a single protein, the 5-HT transporter or SERT, mediates the reuptake of 5-HT from the synaptic cleft and thus the termination of its action. The approved gene symbol for the gene that leads to SERT synthesis is SLC6A4. SLC6A4 is a member of a family of the solute carrier family 6 (neurotransmitter transporter, serotonin), member 4. Human SERT is encoded by a single gene on chromosome 17q11 and is composed of 14 to 15 exons. Transcriptional activity of the SERT gene, SERT availability, and ultimately 5HT reuptake is modulated by a polymorphic repetitive element unique to people and simian primates, the 5HTT gene-linked polymorphic region (5HTTLPR) upstream of the transcription start site. Additional variations have been described in the 5′ untranslated region (5′UTR), in intron 2, and 3′UTR [21].

Neurotransmitter transporters are channel-like proteins that are involved in chemical signaling in the brain and periphery; in fact, they are considered to do the heavy lifting in neurotransmitter inactivation [21,22]. SERT in the gut is similar to that in the brain of the same species [23]. To control 5-HT actions in the gut and limit 5-HT receptor desensitization, both neurons and crypt epithelial cells synthesize SERT proteins [24,25].

Role of serotonin transporter in animal models

In elegant functional studies, Lesch et al showed that, compared with the homozygous long genotype, polymorphic homozygous short and heterozygous genes in the SERT-promoter (SERT-P) were associated with reduced

function of the transporter protein in a lymphoblastoid cell line [26]. Fig. 1 illustrates the potential consequence of a less effective reuptake process for 5-HT, as might occur in a patient with s/s homozygous or l/s heterozygous polymorphism [27].

Serotonin transporter-deficient mice display increased anxiety-related behaviors, and this is thought to be based on increased serotonergic neurotransmission resulting in desensitized and down-regulated 5-HT_{1A} [28], 5-HT_{2A}, or 5-HT_{2C} receptors [29]. GI motility is also abnormal in SERT knockout mice [30]. Adaptive changes occur in the subunit composition of enteric 5-HT_3 receptors in these knockout mice. Such changes are reflected in altered 5-HT_3 receptor affinity and desensitization in the response of the receptor to 5-HT released from enteroendocrine cells [31]. This is manifested in the knockout mice with changes in bowel function, including diarrhea or constipation.

A recent observation suggests that experimental colitis alters 5-HT signaling by decreasing 5-HT reuptake, thereby increasing 5-HT availability [32]. The authors speculated that altered 5-HT availability might contribute to the dysmotility of inflammatory bowel disease, possibly because of desensitization of 5-HT receptors. Coates et al [33] also demonstrated low mucosal SERT and tryptophan hydroxylase mRNA levels in mucosal biopsies from patients with ulcerative colitis or IBS. These data suggest that

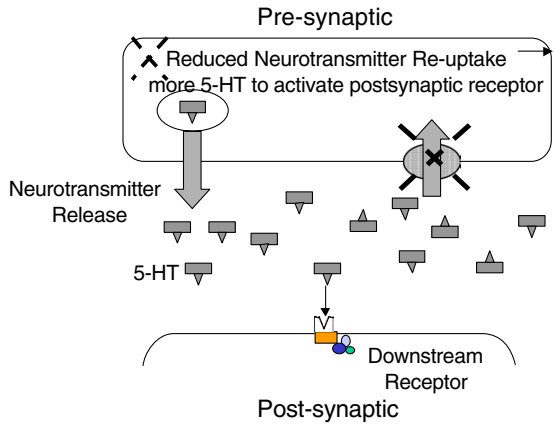

Fig. 1. Ligand receptor interaction at synapse and neurotransmitter reuptake by presynaptic terminal. Differences in the function of the transporter protein are determined genetically and influence the degree of activation of postsynaptic membrane receptors. For example, s/s/ homozygous polymorphism of the SERT-P gene would be expected to reduce the function of SERT and increase the effect of endogenously released 5-HT to activate receptors (eg, 5-HT3 or 5-HT4 receptors on cholinergic neurons to induce colonic contractions or propulsive colonic motility) and potentially lead to symptoms of D-IBS. (*From* Camilleri M. Is there a SERT-ain association with IBS? Gut 2004;53:1396–9; with permission.)

both synthesis and reuptake of 5-HT may be altered, but the relationship with genetic variation is unclear.

Role of serotonin transporter polymorphism in irritable bowel syndrome

Four studies have explored the association of SERT polymorphisms and IBS; results from three of these genetic association studies are summarized in Fig. 2 [27].

The first report was a study from Turkey in 54 patients with IBS (18 with D-IBS) and 91 healthy controls. Pata et al examined possible associations between SERT polymorphisms and the different clinical patterns of IBS. Overall, the distribution of SERT polymorphisms was similar in healthy subjects and the whole group of IBS patients [13]. They observed, however, that the l/s genotype was present in 18 D-IBS patients with a frequency of 88%, whereas none of the patients had the l/l genotype.

The second report by Kim et al at Mayo Clinic studied people residing in the Midwest and explored the distributions of genetic polymorphisms for SERT-P, α_{2C} Del 322-325, and α_{2A} −1291 (C→G) polymorphisms in 274 patients with lower functional GI disorders (FGID) and 120 controls. The distribution of SERT polymorphisms was not significantly different between the patients with lower FGID versus controls (an observation that

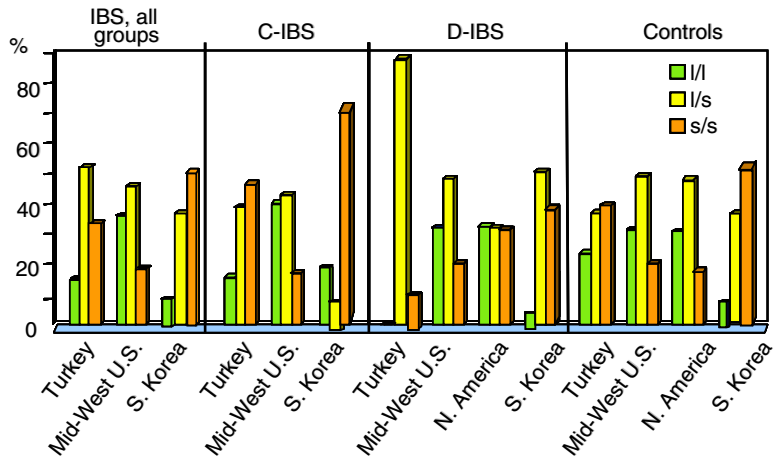

Fig. 2. Proportion of different SERT-P genotypes in patients with different IBS phenotype and healthy controls from several countries. Note that the D-IBS patients in Turkey have predominantly l/s genotype, in contrast to none of the 18 patients with the l/l/ genotype. Note also that controls in the two series from North America have very similar distribution, but the proportions differ from controls in Turkey, suggesting significant racial variation. Finally, note that, in the series of Yeo et al from North America, there are relatively more D-IBS patients with s/s genotype relative to controls, but the actual proportion of the three genotypes in D-IBS was very similar. (*Adapted from* Camilleri M. Is there a SERT-ain association with IBS? Gut 2004;53:1396–9; with permission.)

replicated the result in the whole IBS group studied in Turkey), or between the subset with the phenotype of D-IBS (n = 128) versus controls. In the analysis of 90 C-IBS patients reported by Kim et al, the OR for SERT-P l/s or s/s polymorphisms was not significant (0.7, 95% CI, 0.4, 1.2). This study included a post-hoc analysis to determine whether clinically meaningful associations of the three candidate genotypes could have been detected with at least 80% power. Thus, it was reported that the sample size of the study could detect a difference in prevalence of wild-type (l/l) versus polymorphic (l/s or s/s) genotypes of 12% for all lower FGID, and 19% to 20% for IBS-C and IBS-D. On the other hand, the study identified that combinations of two polymorphisms (α_{2C} Del 322-325 with SERT-P) were associated with high somatic symptom scores [OR = 5.0 (1.11, 22.22)] [11]. This suggests that SERT-P genotype may predispose to somatization or other complex behavioral traits (including fibromyalgia, anxiety, and depression as discussed by Yeo et al [14]) and that studies of interactions between candidate genes that modify motor, sensory, or behavioral functions would be of interest.

The third report from Korea by Lee et al [16] compared SERT-P polymorphisms in 33 IBS patients and 56 healthy controls. The distribution of polymorphisms was not different between the IBS patients and controls, or in IBS patients according to three subtypes based on bowel function.

The fourth report by Yeo et al [14] observed a significant OR of having the s/s genotype in IBS-D patients relative to controls in North America. This observation contrasts with the significant association of IBS-D with the l/s genotype in Turkey. From the function studies performed in vitro [26], however, both l/s and s/s genotype would be predicted to produce SERT molecules with reduced function and therefore result in higher synaptic levels of 5-HT. Whereas the OR provides statistical evidence of an association, it does not prove a disorder in the function of the SERT or that it is causatively related to the development of IBS-D. In fact, the proportions of the l/l, l/s, and s/s genotypes in IBS-D were virtually equivalent in the 194 patients from North America [14].

Potential pitfalls in interpretation of serotonin transporter genotype–phenotype studies

Several potential pitfalls need to be considered in the interpretation of these studies.

Ethnic differences. Difficulties in interpretation of population-based association studies arise because of ethnic differences in SERT-P allele frequencies. The studies discussed previously show the heterogeneity in the distribution of the l/s genotype in different populations. A polymorphism associated with a disorder in one population may not be in another ethnic group. This is a problem that increasingly is being appreciated in behavioral genetics and

may explain, at least in part, several apparently contradictory findings on specific genetic variations observed in different studies. The frequency of the l/l genotype was 6% in Japanese subjects [34,35], 34% in European Americans [26], and 24% in Turks [13]. This variation in background prevalence of a genotype clearly influences the statistical power to detect a genotype-related association.

Racial homogeneity of control and disease groups. In the study by Yeo et al [14], there were no differences in the proportion with l/l genotype in the IBS-D patients and controls. In contrast, there were differences in the distribution of s/s and l/s between controls (17.2% and 47.8%, respectively) and IBS-D (31.4% and 31.9%, respectively). The authors did not provide critically important data on the racial derivation of the patients and controls participating in this study. To attempt to suppress confounding effects such as population stratification and admixture, they included more controls. The proportions in predominantly European Americans of s/s and l/s genotypes of 19% and 49%, respectively in Lesch et al [26] and 20% and 49% in Kim et al [11] suggest that the controls in the paper by Yeo et al [14] were similar to two other independent control cohorts. This is reassuring, because the 448 control DNA samples used by Yeo et al were obtained from three different commercial sources. Thus, female participants predominated in both lower functional GI disorder patients (82%) and controls (79%); European Americans were 89% of controls and 97% of patients, and there were 6% Asians and 3% Hispanics among the healthy participants. Control for ethnic differences is critically important in appraising disease associations between genotype and phenotype.

Interpretation of data from surrogate measurements. Serotonin transporter is found in peripheral sites, including platelets [36]. Because the SERT protein displays the same molecular properties at all known cellular locations [23] and in accordance with the general receptor theory [37], Bellini et al proposed that similar alterations in the 5-HT uptake efficiency also would occur at the intestinal level. SERT was found to be expressed on platelet membranes of 12 IBS-D female patients at a low density (decreased B_{max}), and to display a low degree of affinity (increased K_d) at its ligand binding site when compared with 12 healthy female volunteers [38]. They also suggested a possible correlation between the reduced capacity of serotonin reuptake and the severity of IBS-D symptoms [38]. There are several alternative interpretations of such studies, however. Although the structure and biochemistry of SERT molecules at different sites are similar within the same species, it is unclear whether the results obtained in binding studies of SERT in platelets really reflect the function of enteric SERT. For example, binding studies of SERT in brainstem nuclei may be normal [39] in diseases such as major depression, whereas other studies suggest that platelet SERT function is abnormal in depression [40].

Genetic dissections of complex diseases. Genetic dissections of complex disease are complex. It is conceivable that the impact of the genes may reflect the phenotypic expression of these behavioral or functional disorders [21], and this requires large sample sizes, making the studies laborious and difficult, particularly in IBS, where there is no accepted diagnostic test. IBS also presents significant challenges because of the concurrence of GI and psychological or behavioral phenotype, which may be under the same genetic control. For example, SERT dysfunction may present with a GI phenotype or as a behavioral disorder [41]. Anxiety disorders are commonly part of the comorbidity of IBS [42,43]. SERT dysfunction may contribute to behavioral and functional gut disorders; however, the influence of a single polymorphism on continuously distributed traits is likely to be small in people. More work is needed to assess the influence of genetic variation of SERT in the manifestations and response to therapy [44] of IBS before one can be certain of the importance of SERT for diagnosing and treating IBS.

Alpha-2 adrenoreceptor polymorphisms

Three human α_2 adrenoreceptor subtypes have been cloned and characterized: 2_A, 2_B, and 2_C subtypes [45–48]. Prejunctional α_{2A}- and α_{2C}-adrenoreceptor subtypes regulate the release of norepinephrine from sympathetic nerves through negative feedback at presynaptic nerve endings. It is conceivable that polymorphisms of the genes encoding for these receptors may result in loss of normal synaptic autoinhibitory feedback and enhanced presynaptic release of norepinephrine. As mentioned in the section of SERT polymorphisms, Kim et al [11] reported that two distinct polymorphisms appeared to be independently associated with the phenotype IBS-C: alpha (2C) Del 322-325 (OR, 2.48 [95% CI, 0.98, 6.28]; $P = 0.05$) and alpha (2A) -1291 (C→G) (OR, 1.66 [95% CI, 0.94, 2.92] $P = 0.08$) relative to wild-type. Overall, the alpha (2C) Del 322-325 polymorphism (alone or combined with other polymorphisms) also was associated significantly with a higher somatic symptom score (OR, 2.2 [95% CI, 1.06, 4.64]; $P = 0.03$). Combinations of polymorphisms also were associated with high somatic scores. These studies require replication; their significance to diagnosis and treatment of IBS is unclear.

G protein polymorphism

Metabotrophic (G protein-coupled) receptors mediate slow synaptic transmission. G proteins are composed of different alpha, beta, and gamma subunit isoforms [49]. G protein dysfunctions potentially could block intracellular signal transduction. The gene GNB3 encodes the beta3 subunit of the heterotrimeric G proteins. A polymorphism in the gene gives rise to three possible genotypes: CC, TC, and TT. TC and TT genotypes are associated with the formation of a truncated but functionally active splice

variant, albeit far less active than the normal variant. On the other hand, the CC genotype forms only a minute amount of the beta3 splice variant, and this genotype is characterized by diminished signal transduction responses.

Holtmann et al [12] compared GNB3 genotypes between 112 blood donors and 20 IBS patients and reported that there was no significant association among genotypes in IBS patients. In contrast, there were significant associations in a clinical sample with ulcer-like dyspepsia in blood donors reporting upper abdominal pain.

Implications for diagnosis and treatment

Genetic polymorphisms are common and may have no relevance to disease; therefore, the interpretation of studies of polymorphisms is difficult. Loannidis et al [50] examined the results of 55 meta-analyses of genetic associations and reported that only 16% of genetic associations identified subsequently were replicated with formal statistical significance, without heterogeneity or bias. In genetic association analysis, population stratification can lead to biased or spurious results [51]. Statistical issues also may come into play; some have questioned the appropriateness of a *P* value set at 0.05 in association studies [52].

There have been only two reports about the association of genetic polymorphism with outcome of treatment in IBS patients [44,53]. Camilleri et al [44] analyzed and compared SERT polymorphisms and colonic transit in 30 IBS-D patients who received 1 mg twice a day of alosetron for 6 weeks. They demonstrated that the homozygous long polymorphism of the SERT-P is associated with a greater biological response and the likelihood of a clinically meaningful effect of alosetron, compared with the response in heterozygotes. From the same laboratory, a polymorphism in the CCK-1 intron was associated with the rate of gastric emptying in patients with IBS-C, but no definite influences of this or six other polymorphisms in the CCK-1 receptor or its promoter were associated significantly with response to the CCK-1 receptor antagonist, dexloxiglumide [53].

Summary

Several twin studies and familial aggregation studies in IBS are consistent with either a genetic or a social learning hypothesis, and it is possible that both play a role. The prospect of identifying a genetic cause for IBS may be very important, because it raises the possibility of confirming that IBS is a disease entity, suggests new insight into the pathophysiology of the disorder, and provides new targets for drug development. Several candidate genetic markers including: those related to cytokines such as IL-10, TNF-α and TGF β_1; SERT-P; alpha-adrenergic receptors; and G proteins have been associated with certain aspects of IBS. Genetic polymorphisms,

however, are common and may have no etiological or pathogenetic relevance. Searching for the genes in IBS is of potentially great relevance. Such studies may identify more specific phenotypes in IBS or potentially predict increased disease vulnerability, but it is unlikely that this strategy will lead to a diagnostic test, given the limited component of IBS that is likely to be genetically determined. Pharmacogenomic studies have potential to be important in the future. For this potential to be realized, it will be necessary to formally include genetic studies in trials of experimental drugs. This would enhance understanding of one of the roles of genetics for treating IBS.

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Efficacy of Current Drug Therapies in Irritable Bowel Syndrome: What Works and Does Not Work

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The American College of Gastroenterology's (AGCs) ''Evidence-Based Approach to the Management of Irritable Bowel Syndrome'' [1] defines irritable bowel syndrome (IBS) as abdominal discomfort associated with altered bowel habits. This disorder is characterized by alterations in serotonin signaling and defects in the enteric nervous system, leading to abnormalities in intestinal smooth muscle motility and visceral hypersensitivity (ie, IBS patients experience significant abdominal discomfort with minimal distention of the colonic lumen). Thus, IBS patients complain of multiple symptoms, including constipation, diarrhea, bloating, abdominal discomfort, fecal urgency, straining, and sense of incomplete evacuation, and effective IBS therapies should treat the multiple symptoms of IBS. IBS patients may be classified based upon their predominant bowel symptom: diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), or alternating IBS (A-IBS).

Many treatments are used for patients with IBS, although few treatments have demonstrated efficacy in the management of this disorder. This article reviews the randomized controlled trial (RCT) evidence about the efficacy of bulking agents (eg, psyllium), antispasmodic agents (eg, dicyclomine), tricyclic antidepressant agents (eg, desipramine), selective serotonin reuptake inhibitor (SSRI) antidepressants, 5HT 4 agonists, 5HT3 antagonists, antidiarrheal agents (eg, loperamide), and laxatives (eg, lactulose). The ACGs Functional Gastrointestinal Disorder Task Force completed a comprehensive review of IBS therapies in 2002 [1]. This article updates

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the data in the ACG's monograph, while using a similar system to evaluate the quality of the evidence.

Methods

To identify relevant IBS therapy trials for inclusion in this guideline, MEDLINE searches of English language articles from 1980 to 2004 were performed with different combinations of the following search terms: antispasmodics, antimuscarinics, dicyclomine, hyoscyamine, constipation, fiber, polycarbophil, bulking agents, antidepressants, tricyclic antidepressants, tegaserod, alosetron, antidiarrheal agents, loperamide, SSRIs, irritable bowel syndrome, clinical trial, and randomized (pt). The bibliographies of IBS studies, selected review articles, and selected meta-analyses were searched manually.

The titles and abstracts of all citations identified by the literature search were reviewed. Potentially relevant studies were retrieved, and the selection criteria were applied: (1) randomized controlled trial, (2) population of adult patients with IBS, (3) comparison of IBS therapy versus placebo, (4) evaluation of IBS symptoms, (5) published in English in full manuscript form, and, (6) therapy available in the United States. Data were extracted about: (1) study population, including proportion of female patients; (2) intervention: dosage and schedule of administration of IBS therapy verso placebo; (3) study duration; (4) proportion of patients achieving improvement in IBS symptoms; and (5) adverse events. Data also were extracted about the use of common study design techniques to minimize bias in trials of IBS therapies [2–4] (Box 1). To assess the methodologic strength of individual studies, each criterion in this box was assigned one point on a study design quality scale with a maximum score of 14 points for study design quality. Trials with lower scores are more likely to produce biased and inaccurate results, while trials with higher scores are more likely to produce accurate and unbiased results.

In this analysis and in the ACG analysis [1], improvement in global IBS symptoms was considered the primary outcome of interest. Per the Rome II committee, improvement in global IBS symptoms is probably the most appropriate outcome, because it integrates the multiple symptoms of IBS (eg, bloating, abdominal discomfort, constipation, or diarrhea) into a single outcome [2]. Nevertheless, data about individual IBS symptoms, including stool frequency and stool consistency, also provides useful information, so data about individual IBS symptoms also were extracted. Because of wide variation in study designs, no attempt was made to combine results into a meta-analysis.

Antispasmodic agents

IBS is characterized by dysfunction of intestinal smooth muscle activity and visceral hypersensitivity, which produces symptoms of abdominal

Box 1. Quantitative assessment of study methodology scale

Use Rome criteria to identify patients with IBS.
Randomization
Parallel study design (ie, no crossover studies)
Double-blinding
Complete follow-up of patients
No placebo run-in
Baseline observation of patients to assess symptoms
Treatment duration of 8 to 12 weeks
Follow-up after treatment to assess symptoms
Compliance with the treatment is measured
Sample size calculation is provided, and adequate sample size enrolled.
Primary outcome of the trial is improvement in global IBS symptoms.
Primary outcome is based on patient assessment.
Validated scale used to measure improvement in IBS symptoms.

Adapted from Van Zanten SJO, Talley N, Bytzer P, et al. Design of treatment trials for functional gastrointestinal disorders. Gut 1999;45(Suppl 2):II69–77.

The members of the Committee on Design of Treatment Trials for Functional Gastrointestinal Disorders of the Rome II committee also noted additional recommendations for the design of clinical trials, including a priori-defined study endpoint and definition of patient setting (primary care versus tertiary care). Published reports of studies, however, rarely provided adequate information to assess the use of these additional techniques in the conduct of treatment trials. Therefore, these additional recommendations were not included in the scale.

discomfort and altered bowel habits. Antispasmodic agents decrease intestinal smooth muscle activity, which might decrease abdominal discomfort if this pain is secondary to spasm of the intestinal smooth muscle. There are two types of antispasmodic agents: direct smooth muscle relaxation agents (eg, mebeverine, pinaverine) and anticholinergic/antimuscarinic agents (eg, dicyclomine, hyoscyamine) [5–21].

Direct smooth muscle relaxants are available in Europe, Mexico, and Canada, but they are not available in the United States. Multiple small RCTs have examined the efficacy of these agents, including mebeverine, pinaverine, and otilinium [6,7,9–22]. Most of these studies demonstrate poor study design (eg, enrolled an inadequate sample size; study endpoints were vague or defined by physicians instead of patients; blinding was inadequate, or cross-over design was used), and individual RCTs produced conflicting results. Because these agents are not available in the United States,

a complete discussion of these agents is not included. Meta-analyses [23,24], however, indicate that mebeverine and pinaverine are probably effective at improving some IBS symptoms, although the weak study design of individual studies limits the strength of recommendations based upon these data.

Only three RCTs [5,8,16] have examined the efficacy of anticholinergic/antimuscarinic agents (eg, levsin) available in the United States (Table 1). These trials demonstrated poor study design. Appropriate definitions of IBS patients were not used; inadequate sample sizes of patients were enrolled, and trials were very short (no more than 4 weeks). In the first two studies [5,16], no significant difference in outcomes was noted between patients treated with the active drug versus placebo. Also, one large (n = 360), non-English language trial did not meet criteria for inclusion in this article, but it found no difference between hyoscyamine and placebo for relief of abdominal pain or abdominal distention and no significant difference for global IBS symptom improvement [25]. A single study [8] demonstrated a statistically significant improvement in global IBS symptoms with dicyclomine compared with placebo, but this study used a supratherapeutic dose of dicyclomine hydrochloride 40 mg four times daily, which also produced significantly more adverse events among dicyclomine-using patients versus placebo-using patients (69% versus 16%, respectively, $p < 0.01$). Because of

Table 1
Trial characteristics: antispasmodic agents

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Outcome measures	Quality score (range: 0–14)
Wheatley [5]	Dicyclomine versus placebo	20 mg three times daily	Crossover	29	Individual IBS symptoms (assessed by investigator)	5
Page [8]	Dicyclomine versus placebo	40 mg four times daily	Parallel	71	Global IBS symptom improvement and individual IBS symptoms	5
Ritchie [16]	Hyoscyamine versus ispaghula husk versus lorazepam versus placebo	10 mg four times daily	Parallel	96	Global IBS symptom improvement (assessed together by investigator and patient)	7

Adapted from Brandt L, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 2002;97: S7–26; with permission.

these adverse events, 15% of dicyclomine-treated patients withdrew from study, while no placebo-treated patients withdrew. This is not surprising, because with increasing doses these agents may exhibit atropine-like adverse effects including vision disturbances, urinary retention, dry mouth, and constipation. This last effect should be emphasized, because many IBS patients may have constipation as a predominant bowel symptom, and the smooth muscle relaxant properties of these agents may exacerbate the underlying constipation.

Based upon these data, antispasmodic agents available in the United States appear to be similar to placebo. Any benefit observed among patients with IBS treated with these agents is probably consistent with a placebo effect. The author does not prescribe antispasmodic agents for IBS patients as a new agent because of this evidence. If a patient is already using antispasmodic agents and believes that these agents are beneficial, then the author does not discontinue the medication.

Bulking agents

The category of bulking agents includes various forms of fiber, including, psyllium, methylcellulose, corn fiber, calcium polycarbophil, and ispaghula husk, which is the outer coat or husk of the psyllium seed. Because these agents provide bulk to stool, they have been recommended as a treatment for IBS to increase stool frequency and ease stool passage.

Thirteen RCTs have evaluated the effectiveness of bulking agents for treating IBS [26–38] (Table 2). Generally, these trials exhibited poor study design, including inadequate sample sizes of patients, poorly specified symptom definitions of IBS patients, short study duration (no more than 4 weeks), or use of global IBS symptom improvement as the primary outcome.

In a single study, corn fiber and placebo improved pain severity, stool frequency, and stool consistency by similar amounts [26]. In a single study, calcium polycarbophil reported a preference with calcium polycarbophil over placebo among patients with C-IBS or A-IBS, but no significant difference in overall preference and no difference in abdominal discomfort. It is unclear if the difference in C-IBS patients and A-IBS patients merely reflects improvement in stool frequency or truly represents an improvement in global IBS symptoms [32]. Of the four placebo-controlled studies of wheat bran [27,29–31], the results for wheat bran and placebo were very similar. In a single study of psyllium [33], there was no significant difference between psyllium, although symptoms were improved in over 70% of patients in both groups. In five studies of isphaghula husk [34–38], global satisfaction with bowel habits and ease of stool passage was improved with isphagula husk compared with placebo in four studies, but abdominal pain was not improved.

Table 2
Trial characteristics: bulking agents

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Duration	Outcome measures	Quality score (range: 0–14)
Longstreth [33]	Psyllium	6.4 g three times daily	Parallel	60 (83%)	8 weeks	Sxs, SGA	9
Arthurs [36]	Ispaghula/poloxamer	2 sachets per day	Parallel	78 (78%)	4 weeks	SGA	7
Arffmann [29]	Wheat bran	15 g twice daily	Crossover	18 (78%)	6 weeks	Sxs	5
Prior [37]	Ispaghula	1 sachet three times daily	Parallel	80 (90%)	12 weeks	Sxs, SGA	9
Lucey [30]	Wheat bran	12.8 g per day	Crossover	28 (68%)	3 months	Sx score	6
Cook [26]	Corn fiber	10 g twice daily	Crossover	9 (89%)	12 weeks	IBSQ, Sxs	8
Toskes [32]	Calcium polycarb.	1.5 g four times daily	Crossover	23 (70%)	12 weeks	SGA, Sxs	7
Snook [31]	Wheat bran	40 g/d	Crossover	71	7 weeks	SGA, Sxs	6
Soltoft [27]	Wheat bran	30 g/d	Parallel	52 (65%)	6 weeks	SGA, Sxs	6
Manning [28]	Wheat fiber	20 g/d	Parallel	24 (50%)	6 weeks	Sxs	5
Ritchie [34]	Ispaghula husk	1 sachet twice daily	Parallel	24	3 months	SGA	7
Jalihal [38]	Ispaghula husk	30 g sachet daily	Crossover	20 (20%)	4 weeks	SGA, Sxs	7
Golechha [35]	Ispaghula husk	?	Crossover	26	3 weeks	SGA	6

Abbreviations: SGA, global ISB symptom improvement; Sxs, individual IBS symptoms.

Adapted from Brandt L, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol 2002;97:S7–26; with permission.

A recent meta-analysis [39] suggested that soluble types of fiber (eg, psyllium, isphagula husk, and calcium polycarbophil) may be effective at improving global IBS symptoms. This meta-analysis, however, should be interpreted very cautiously. Tests of heterogeneity, which determine if studies produce similar results, produced significant results for all analyses. This means that study results were so divergent that it is probably inappropriate to combine the results in a meta-analysis, because study design was quite different between individual studies. Also, the investigators extrapolated endpoints about global satisfaction with bowel habits to represent global satisfaction with IBS symptoms, although global satisfaction with bowel habits does not encompass improvement in abdominal discomfort.

No adverse event data were reported in the bulking agent RCTs. Clinicians, however, should be aware of several potential adverse events. First, metabolism of bulking agents by gut bacteria produces bowel gas [40,41], which may increase bloating and exacerbate abdominal discomfort in patients with IBS [42,43]. Different bulking agents, including psyllium, have been associated with anaphylactic reactions, esophageal obstruction, and bowel obstruction when used in large quantities without sufficient water [44].

Based upon these data, bulking agents appear to be similar to placebo. Any benefit observed among IBS patients treated with these agents is probably consistent with a placebo effect. The author does not prescribe bulking agents for IBS patients. I believe that relatively high doses of bulking agents are needed to increase stool frequency and that higher doses produce clinically important abdominal discomfort and bloating. The author does prescribe bulking agents for patients with chronic constipation, characterized by straining, hard pellet-like stools, and sense of incomplete evacuation without abdominal discomfort.

Antidiarrheal agents

Patients with D-IBS demonstrate accelerated intestinal transit [45], and antidiarrheal agents may delay intestinal transit. Three RCTs [46–48] evaluated the effectiveness of loperamide for treating IBS (Table 3). These trials used poor study design, including small sample sizes and short duration (no more than 5 weeks). Additionally, Rome criteria were not used to identify patients with IBS. These RCTs do indicate that loperamide is significantly better than placebo at decreasing stool frequency and improving stool consistency among patients with IBS [46–48]. Loperamide decreased stool frequency from 1.9 times per day to 1.3 times per day, decreased the percentage of unformed stools from 60% to 31%, and decreased the incidence of urgency from 2.4 days per week to 1.1 days per week [46]. Stool frequency was decreased (35% versus 10%), stool consistency was improved (50% versus 20%) [48]. Additionally, stool

Table 3
Trial characteristics: antidiarrheal agents

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Duration	Outcome measures	Quality score (range: 0–14)
Cann [46]	Loperamide	2–12 mg daily	Crossover	28 (75%)	5 weeks	Sxs, SGA	7
Hovdenak [47]	Loperamide	4 mg	Parallel	58	3 weeks	Sxs, SGA	6
Efskind [48]	Loperamide	2–6 mg daily	Parallel	69 (80%)	5 weeks	Sxs	5

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frequency (100% versus 40%), stool consistency (100% versus 50%), and overall symptoms (100% versus 25%) were improved in patients with painless diarrhea [47]. None of the studies, however, demonstrated significant improvement in abdominal distension, abdominal pain, or global IBS symptoms. Furthermore, when subgroups of IBS patients (eg, C-IBS) were examined, improvement in stool frequency and stool consistency was limited to patients with D-IBS. These RCTs did not report specific data about adverse events.

Based upon these data, loperamide appears to be more effective than placebo at improving stool consistency and decreasing stool frequency among D-IBS patients and patients with painless diarrhea. They are not more effective than placebo at improving abdominal discomfort or global IBS symptoms, however. The author uses tricyclic antidepressants as primary therapy for D-IBS and prescribes loperamide as an adjunctive agent for the treatment of this disorder. I allow my patients to use loperamide as needed for their diarrhea symptoms.

5HT4 receptor agonists (ie, tegaserod)

Tegaserod is a 5HT4 receptor agonist that stimulates the peristaltic reflex, increases small intestine and colonic transit, and mediates visceral hypersensitivity by reducing activity of colonic afferent nerves [49–51]. Through these mechanisms, it should be effective for altered bowel habits and abdominal discomfort in nondiarrhea-predominant IBS. Tegaserod is approved by the Food and Drug Administration (FDA) for treating C-IBS in women. The recommended dosage is 6 mg twice daily, and the following analysis is limited to results achieved with this dose.

Six RCTs have evaluated the effectiveness of tegaserod 6 mg twice daily for managing IBS [49,52–57] (Table 4). All of these trials met essentially all of the Rome committee criteria for the appropriate design of IBS therapy

Table 4
Trial characteristics: 5-HT receptor agonists (ie, tegaserod)

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Study duration	Outcome measures	Quality score (range: 0–14)
Muller-Lissner [52]	Tegaserod versus placebo	6 mg twice daily or 2 mg twice daily	Parallel	881 (83% female)	12 weeks	Global IBS sx. improvement, individual IBS	12
Whorwell [53]	Tegaserod versus placebo	6 mg twice daily or 2 mg twice daily	Parallel	799 (87% female)	12 weeks	Global IBS sx. improvement, individual IBS symptoms, adverse events	12
Novick [55]	Tegaserod versus placebo	6 mg twice daily	Parallel	1519 (100% female)	12 weeks	Global IBS sx. improvement, individual IBS symptoms, adverse events	13
Kellow [56]	Tegaserod versus placebo	6 mg twice daily	Parallel	520 (88% female)	12 weeks	Global IBS sx. improvement, individual IBS symptoms, adverse events	13

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trials, including appropriate use of Rome committee criteria for identification of IBS patients, adequate sample size, adequate study duration, and appropriate study endpoints. More than 80% of the patient population was women, and most met criteria for C-IBS, although a few patients in all trials had A-IBS. All six trials demonstrated statistically significant improvement in global IBS symptoms for tegaserod-using patients compared with placebo-using patients. Based on a longitudinal analysis, approximately 10% more patients using tegaserod experienced improvement in global IBS symptoms compared with placebo-using patients. Based on generalized estimating equations, tegaserod-using patients were significantly more likely to consistently demonstrate improvement in global IBS symptoms during the first 4 weeks of the trial (odds ratio [OR], 1.89 to 2.61) [56,57]. In subgroup analysis, tegaserod-using patients demonstrated significantly less bloating and abdominal discomfort and improved bowel habits compared with placebo-using patients, based on likert scale and visual analog scale measurements.

Diarrhea is the most common adverse event associated with tegaserod use. In RCTs, it is reported in approximately 9% of tegaserod-using patients [58], although fewer than 2% of patients stop tegaserod because of diarrhea. In pooled analysis of RCTs, headaches occur slightly more frequently with tegaeserod than placebo (15% versus 12%, respectively, $p < 0.05$). No other adverse events occur with more frequency among tegaserod-using patients compared with placebo-using patients. Although ischemic colitis has been demonstrated with alosetron use (a 5HT3 receptor antagonist for treatment of D-IBS), the rate of ischemic colitis is numerically higher with placebo than tegaserod in controlled trials. No episodes of ischemic colitis have been reported among over 11,000 patients treated for over 3500 patient-years in controlled trials.

Based upon these data, tegaserod is more effective than placebo at improving global IBS symptoms, bloating, abdominal discomfort, and altered bowel habits among patients with C-IBS. The author uses tegaserod as primary therapy for nondiarrhea-predominant IBS. Osmotic laxatives are prescribed as an adjunctive agent, allowing patients to use magnesium hydroxide (ie, milk of magnesia) as needed for their constipation symptoms.

Osmotic laxatives

Patients with C-IBS demonstrate delayed intestinal transit, so osmotic laxatives could be useful to manage IBS symptoms. There are no RCTs examining the efficacy of osmotic laxatives (eg, lactulose, PEG-3350, magnesium hydroxide or milk of magnesia) in IBS patients, however. Therefore, an evidence-based conclusion about the efficacy of osmotic laxatives for managing IBS is not possible. If an appropriately designed study was performed, then osmotic laxatives may be useful. In the absence

of appropriate evidence, however, clinicians should use agents proven effective for C-IBS as first-line therapy.

Antidepressants

Patients with IBS demonstrate visceral hypersensitivity: elevated levels of discomfort with minimal distention of the intestine. Since tricyclic antidepressants are effective therapies for chronic pain syndromes; they have been promoted as potential treatments for the abdominal discomfort of IBS. Eight RCTs [59–66] and one meta-analysis [67] have evaluated the efficacy of tricyclic antidepressants in IBS (Table 5). Most used poor study design, including small sample sizes and short duration (no more than 5 weeks). Additionally, Rome criteria were not used to identify IBS patients. Four of these RCTs demonstrated that tricyclic antidepressant agents are significantly better than placebo at improving abdominal discomfort, but only one of these studies demonstrated significant improvement in global IBS symptoms.

Drossman et al [66] performed a rigorous RCT that meets essentially all Rome criteria for appropriate design of an IBS therapy, and the results from this study are most illustrative of the risks and benefits of treating IBS with a tricyclic antidepressant. In this trial, desipramine was compared with placebo in 216 patients. In the per-protocol analysis, there was no significant difference between desipramine and placebo (60% versus 47%, respectively, $p = 0.16$), which most likely results from the 25% of desipramine-treated patients who discontinued medication because of adverse events (ie, dry

Table 5
Trial characteristics: antidepressant agents

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Study duration	Outcome measures	Quality score (range: 0–14)
Heefner [59]	Desipramine	150 mg qhs	Parallel	44	8 weeks	Sxs	6
Steinhart [60]	Amitriptyline	50 mg qhs	Crossover	14 (79%)	4 weeks	Sxs	6
Myren [61]	Trimipramine	25 mg qhs	Parallel	61 (54%)	4 weeks	Sxs	5
Myren [62]	Trimipramine	50 mg qhs 35 mg qhs 40/10 mg 10 mg three times daily	Parallel	428 (50%)	6 weeks	Sxs	5
Greembaum [63]	Desipramine	150 daily	Crossover	41 (66%)	6 weeks	Sxs	5
Vij [64]	Doxepin	75 mg qhs	Parallel	50 (28%)	6 weeks	Sxs	5

Abbreviations: Sxs, individual IBS symptoms; qhs, before sleep.

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mouth, dizziness, and constipation). As an anticholinergic agent, tricyclic antidepressants cause constipation as the dosage is increased. A preplanned subgroup analysis evaluated patients with D-IBS versus patients with C-IBS. This analysis demonstrated significant improvement in patients with D-IBS, but no improvement in patients with C-IBS.

Based upon these data, tricyclic antidepressants appear to be more effective than placebo at improving abdominal discomfort in patients with IBS. Tricyclic antidepressants also appear to improve global IBS symptoms among patients with D-IBS, although this effect is absent in patients with C-IBS. Because this observation probably reflects the constipating effect of increasing doses of tricyclic antidepressants, the author uses tricyclic antidepressants as primary therapy for D-IBS and prescribes loperamide as an adjunctive agent for the treatment of this disorder. I allow my patients to use loperamide as needed for diarrhea symptoms.

5HT3 receptor antagonists

Alosetron is a 5HT3 receptor antagonist that decreases small intestine and colonic transit and mediates colonic afferent nerve activity [68,69]. Through these mechanisms, it should be effective for altered bowel habits and abdominal discomfort in D-IBS. Alosetron is approved by the FDA for treating severe D-IBS in women who have failed conventional therapies. Alosetron is limited to this indication because of an association with ischemic colitis and serious complications of constipation.

Multiple RCTs [70–73] have evaluated the effectiveness of alosetron for managing IBS (Table 6). All trials met most Rome committee criteria for the appropriate design of IBS therapy trials, including appropriate sample size, appropriate patient definitions, and appropriate study duration. The patient population was more than 80% women, and most met criteria for D-IBS. All trials demonstrated statistically significant improvement in stool frequency, stool consistency, and abdominal discomfort. When global IBS symptoms were measured, alosetron-using patients experienced significant improvement compared with placebo-using patients (76% versus 44%, respectively; $p < 0.05$). The magnitude of abdominal discomfort improvement varied from 10% to 27% for alosetron-using patients versus placebo-using patients. In subgroup analysis, alosetron-using patients demonstrated significantly less fecal urgency and stool frequency compared with placebo-using patients, based on likert scale and visual analog scale measurements.

Constipation is the most common adverse event associated with alosetron use. In RCTs, it is reported in up to 39% of alosetron-using patients [1], and up to 10% of patients stopped alosetron because of diarrhea. In pooled analysis of clinical trials, ischemic colitis occurs more frequently with alosetron than with placebo (0.15% versus 0.0%, respectively, $p = 0.03$) [74]. All cases of ischemic colitis, however, were cases of reversible colonic ischemia without long-term sequelae. Serious complications of constipation

Table 6
Trial characteristics: 5HT3 receptor antagonists

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Study duration	Outcome measures	Quality score (range: 0–14)
Camilleri [70]	Alosetron versus placebo	1, 2, 4 or 8 mg twice daily	Parallel	370 (53% female)	12 weeks	Individual IBS symptoms, adverse events	12
Jones [71]	Alosetron versus mebeverine	Alosteron 1 mg twice daily versus Mebeverine 135 mg three times daily	Parallel	623 (100% female)	12 weeks	Individual IBS symptoms, adverse events	12
Camilleri [72]	Alosetron versus placebo	1 mg twice daily	Parallel	647 (100% female)	12 weeks	Individual IBS symptoms, adverse events	12
Lembo [73]	Alosteron versus placebo	1 mg twice daily	Parallel	801 (100% female)	12 weeks	Individual IBS symptoms, global IBS symptom improvement, adverse events	12

Primary outcome measure was relief of abdominal pain in three trials [70–72] and was relief of fecal urgency in one trial [73].

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(eg, hospitalization or surgery because of severe constipation) occurred with similar frequency in alosetron-using patients and placebo-using patients in clinical trials [75]. In postmarketing surveillance, the rate of ischemic colitis in alosetron-using patients was 0.66 per 1000 patient-years, and the rate of serious complications of constipation was 1.1 per 1000 patient-years [74,75].

Based upon these data, alosetron is more effective than placebo at improving global IBS symptoms, abdominal discomfort, stool consistency, and stool frequency among women with D-IBS. The author uses alosetron as secondary therapy for patients with D-IBS who have failed therapy with tricyclic antidepressants and loperamide.

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Potential future therapies for Irritable Bowel Syndrome: Will Disease Modifying Therapy as Opposed to Symptomatic Control Become a Reality?

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Although many trials appear to contain patients who have had symptoms for many years, such chronic patients may not be typical. Cohort studies and a recent meta-analysis [1] suggest that up to 50% of patients recover during follow-up. An early study found that a short history (less than 1 year), an infective cause, and absence of adverse psychological factors [2] were all favorable features. Subsequent studies have confirmed these findings [3,4] and also that with resolution of chronic life difficulties such as divorce, imprisonment, or bankruptcy, some patients with irritable bowel syndrome (IBS) improve significantly [6]. These observations of spontaneous cures encourage clinicians to believe that treatment of underlying causes might affect a cure in some patients.

Mechanisms of disease

The most prominent symptoms in IBS are pain, discomfort, and bloating, which involve interpretation at a cortical level of signals originating in the gut. Mechanisms and possible treatments therefore can be considered according to the level at which signaling becomes abnormal, starting at the level of the gut and finishing in the secondary association areas of the cerebral cortex (Box 1).

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Box 1. Mechanisms and treatment of IBS

Level	Mechanism	Possible Treatments
Gut lumen	Physical/chemical	Dietary
	Stimulation by food, gas	Antibiotics
		Probiotics
Gut mucosa	Inflammation	Anti-inflammatory
	Altered afferent signalling	Mast cell stabilisers
	(enteroendocrine, mast cells)	Probiotics
Spinal cord	Central sensitisation	NMDA antagonists

Diet and irritable bowel syndrome

Many patients experience exacerbation of their symptoms in the postprandial period [5] and are convinced of the link between food and symptoms, often avoiding certain foods with the aim of reducing symptoms. Gastrointestinal secretions stimulated by food amount to more than 7 L in response to ingestion of less than 1 L of food [6]. Plainly, even a relatively modest degree of malabsorption of lactose or other osmotically active sugars such as fructose will cause exaggerated intestinal distension by fluid [7]. Further sources of distension included swallowed gas and also gas generated by fermentation of malabsorbed carbohydrate in the colon. IBS patients appear to be less able to propel such gas through the gut causing intestinal distension and symptoms of bloating and pain [8]. Finally, food may induce an immune response that contributes to mucosal inflammation and hence sensitization of visceral afferents.

Evidence that lactose free diets can cure irritable bowel syndrome?

Many patients with IBS who believe they are lactose intolerant are not lactose malabsorbers [15]. Furthermore, even if lactose malabsorption is identified objectively and a lactose-free diet instituted, the benefit is minimal in most series [9,10]. When lactose malabsorbers underwent a double-blind trial of 240 mL of a lactose-containing or lactose-free milk, symptoms were no different on the two diets [11]. Many patients ingest less than 240 mL of milk per day and for them at least, identifying lactose malabsorption is likely to be of no value. Where intake is high, as in the Netherlands, however, lactose exclusion may help some [12]. One group of patients in which lactose intolerance might be considered to be more significant is in those with postinfectious IBS. About 5% of children with chronic diarrhea after viral gastroenteritis have significant lactose malabsorption [13]. In adults, however, this does not appear to be the case, and a recent study of IBS developing after bacterial gastroenteritis found no cases of lactose intolerance [14].

Evidence that exclusion diets can help irritable bowel syndrome symptoms

Several authors have used an empirical approach to modifying diet using exclusion of commonly offending items followed by reintroduction of individual items with the aim of identifying foods causing IBS symptoms [15]. The most common items identified are usually milk, wheat, and eggs, with coffee, nuts, and peas less frequent [16]. One of the largest studies found 91 of 189 patients with IBS who undertook a trial of exclusion diet improved, and 73 out of the 91 identified specific food intolerances. Seventy-two of 73 patients remained symptom-free on their diet during follow-up at a mean (standard deviation [SD]) of 12.5 (8) months [17]. Other smaller studies identified similar types of food but have given response rates varying from 67% [18] to 15% [19]. Few of these studies excluded lactose malabsorption in those reporting milk intolerance, but the other studies already discussed suggest that this is unlikely to be the basis of the response observed in most cases.

Evidence that altering intestinal gas can alleviate irritable bowel syndrome symptoms

Dietary means

Colonic gas production depends on delivery of fermentable carbohydrate to the colon and the colonic bacterial flora. Using a metabolic tent to assess total gas excretion, King et al [20] showed increased total hydrogen excretion in IBS patients, which was reduced by a diet that excluded a range of potentially poorly absorbed carbohydrates including wheat, potatoes, onions, and dairy products. After 2 weeks of the exclusion diet, the hydrogen generated from a standard oral dose of lactulose was reduced substantially, indicating a diet-induced change in the colonic bacterial flora [20].

Probiotics

More direct manipulation of colonic flora would be possible by means of probiotics, and these have been studied extensively in irritable bowel disease (IBD). Evidence of benefit in IBS, however, is conflicting [21]. A randomized placebo-controlled trial of *Lactobacillus plantarum* verses placebo showed a small reduction in flatulence compared with placebo [22]. A second study with *L. plantarum* [23] showed a more substantial benefit. A study with VSL3, a probiotic previously shown to be effective in the treatment of pouchitis, showed only a marginal improvement in bloating and no changes in other symptoms, however [24]. *L. plantarum* does not alter 24-hour gas excretion compared with placebo [25]; however this study was, by its intensive nature, restricted to just 12 patients and may have suffered from a type II error.

Immunological response to food

Allergic responses to food with asthma and urticaria mediated by IgE antibodies are recognized by dermatologists and immunologists and rarely present to gastroenterologists. Non-IgE-mediated immune responses, however, also may cause food intolerance. A T-cell mediated response to dietary gliadin causes celiac disease, which can mimic IBS, and occurs in 3% of patients with IBS symptoms [26]. The predisposing human leukocyte antigen (HLA) allele, HLA-DQ2, is found in nearly one third of the normal population, so it is possible that forme fruste of celiac disease exist which lack villous atrophy but still cause a low-grade immune response. This might explain why in a study of patients with unexplained diarrhea, those with HLA-DQ2 appeared to respond to an open-label gluten-free diet, while those who were DQ2-negative did not [27].

Evidence that exclusion diets or cromoglycate can prevent immune response to food

Early reports suggested that exclusion diets could identify foods to which IBS patients showed an inflammatory response [28], but subsequent studies were unable to link a positive response on double-blind challenge to positive skin prick tests or the presence of food antibodies in serum [29,30]. Furthermore, a large recent survey found only 11 of 80 patients had positive skin prick tests to foods they reported intolerance too [31]. It may be that detecting a local immune response to food antigens requires a more direct approach as was used by Bischoff, who injected food antigens submucosally, inducing a wheal and flare reaction in patients with IBS but not controls [32]. This local mucosal response was associated with activation of mast cells and eosinophils, but not associated with serum IgE or skin prick tests, which may explain the poor predictive value of such tests. Furthermore this open-label study reported that excluding the offending food and additional cromoglycate or rarely low-dose prednisolone produced improvement in most patients. There is one double-blind [33] and several open-label trials reporting a response to cromoglycate in diarrhea-predominant IBS [34–36], suggesting that mast cells may play an important role. Because it seems unlikely that this is by means of an IgE-linked activation, other mediators such as neural influences need to be considered. Animal models [37,38] and some human studies [39] indicate that stress can activate mast cells, which might explain some of the response to cromoglycate.

More recently, the possibility that an IgG response might mediate an abnormal reaction to food in IBD patients has been explored using exclusion diets based on presence of food IgG antibodies to common food antigens. Patients showed a significantly greater improvement on an exclusion diet that avoided food to which they had circulating IgG antibodies when compared with a control diet in which the exclusions were

unrelated to the patients' antibodies [40]. However, because 84% had antibodies to milk, and 49% antibodies to wheat, the exclusion diets were quite similar, so the benefit may have been unrelated to the presence of antibodies and simply because of excluding wheat and dairy products.

Changes in the gut mucosa

Evidence of peripheral inflammation in irritable bowel syndrome

There are several recent studies indicating that patients with IBS, particularly postinfective IBS and diarrhea (D)-IBS have evidence of immune activation compared with healthy controls [41]. Table 1 shows that many studies show that CD3 + lymphocytes are increased in D-IBS and that subsequent studies have shown increase in mucosal interleukin (IL)-1β mRNA [42,43]. This suggests a failure of down-regulation of the normal lymphocyte response to infection, possibly by means of inadequate IL-10 response [44]. This is supported by genetic evidence indicating that high IL-10 and transforming growth factor (TGF)-β producers, which would tend to have more effective T regulatory cells tend to be less common in patients with IBS [45]. Only the author's group has examined the serotonin-containing enterochromaffin (EC) cells and found them to be increased. There are extensive animal data, however, suggesting that this is a common feature of the mucosal response to acute inflammation [46,47]. Indeed, when biopsies were taken at 2 weeks postinfection, 85% of individuals infected were shown to have increased EC cells [48]. Macrophages [48] and mast cells also increase, although as Table 1 indicates, the mast cell response is most obvious more proximally, particularly in the terminal ileum. Further

Table 1
Mucosal markers of inflammation in irritable bowel syndrome by subtype and site of biopsy

Author and date	Sub type of IBS	Site of biopsy	CD3 + lymphocyte	EC cells	Mast cells
Weston 1993 [117]	D-IBS	T. Ileum	+	NA	++
O'Sullivan 2000 [118]	D-IBS	Caecum	NA	NA	++
Gwee 1999 [119]	P-IBS	Rectum	++	NA	NA
Spiller 2000 [48]	P-IBS	Rectum	++	++	-
Chadwick 2003 [120]	D-IBS	Colon	++	NA	-
Dunlop 2003 [121]	P-IBS	Rectum	++	++	-
Dunlop 2003 [84]	Non-PI-IBS	Rectum	++	-	+
Wang 2004 [43]	P-IBS and D-IBS	T. Ileum colon	++ ++	NA	+ -
Barbara 2004 [49]	C-IBS and D-IBS	Descending colon	NA	NA	++

Abbreviations: NA, not assessed; D-IBS, diarrhea-predominant IBS; P-IBS, postinfective IBS.

Increase compared with control ++ = significantly, + = minor increase, - = NS.

studies recently published have indicated increased mast cells in the descending colon of unselected IBS patients [49], but this needs reproducing.

Mucosal Inflammation and visceral hypersensitivity

Part of the interest in low-grade inflammation in the gut mucosa has been the convincing experimental evidence that inflammation activates visceral afferents and sensitizes them [50]. Possible mediators include prostaglandins, bradykinin, nerve growth factor, adenosin tri-phosphate, and serotonin [51]. Preliminary data showing that supernatants of IBS biopsies activate enteric nerves add weight to the idea that this might be relevant to IBS [43].

Therapies aimed at reducing mucosal inflammation

Immunosuppressants

Enterochromaffin hyperplasia appears, like Paneth cell hyperplasia [52], to be driven largely by T cells. Animal studies showed that immunosuppression with hydrocortisone would prevent EC hyperplasia [53]. This finding led the author to perform the only randomized controlled trial (RCT) of prednisolone in post infective (PI)-IBS [54]. Prednisolone 30 mg was given for 3 weeks to PI-IBS patients 3 months after the initiating *Campylobacter* infection. Although prednisolone accelerated the decline in T lymphocytes, it did not alter EC cell numbers, nor significantly improve symptoms [54]. EC cells have a much slower turnover [55], than lymphocytes so it may be that the treatment was of too short a duration. The patients, however, were reluctant to take prednisolone and one can be confident that if such a treatment is to be acceptable it would have to be using an anti-inflammatory agent with a much better adverse effect/risk benefit ratio than prednisolone.

Inhibitors of mast cell activation

Mast cell hyperplasia following infection is, at least in animals, T-cell driven, so anti-inflammatory treatments also might be effective here. There are no data, however, at present. Animal studies suggest that stress can activate mast cells, but whether stress-relieving therapies might alter mast cell activation in people has not been studied. As discussed previously, there are several reports of benefit of cromoglycate therapy in diarrhea-predominant IBS [33–36,56], but methodological inadequacies mean that these studies need confirmation.

Probiotics as anti-inflammatory treatments

Recent studies have suggested that probiotics alter immune responsiveness [57,58]. The beneficial effects in inflammatory bowel disease can be observed even with dead bacteria, suggesting that the mode of action might be more a systemic alteration in immune response rather than a local one at

the level of the gut lumen [59,60]. Recent studies have shown that *L. paracasei* normalized muscle hypercontractility in a murine model of postinfectious IBS [61], an effect that probably depends on down-regulation of the immune response. As already discussed, probiotics remain an area of great but as yet unfulfilled therapeutic promise.

Evidence of central sensitization in irritable bowel syndrome

The concept of secondary hyperalgesia or alodynia, whereby inflammation of one area can lead to hypersensitivity of an adjoining noninflammed area, is established in somatic pain. The mechanism is uncertain but involves cross-talk between visceral nociceptive afferents and somatic afferents, with increased synaptic activity in the spinal cord dorsal horn leading to increased excitability of the second-order neurones [62], which receive input from visceral afferents and nerves innervating the skin. This viscerosomatic convergence leads to visceral pain being referred (ie, perceived as originating in the abdominal wall). Colonic inflammation expands the cutaneous area that excites these second-order viscerosomatic neurones [63]. Abnormally extensive referral patterns in response to colorectal distension also are seen in IBS [64]. Thus pain from rectal distension is perceived both perianally (as is normal) and also periumbilically [65]. Although there are no human models of experimental colonic inflammation, recent human studies have shown that acid infusions into the lower esophagus sensitize responses to electrical stimulation of the upper esophagus [66]. This indicates that central sensitization can be induced in people, and this process was exaggerated in patients with noncardiac chest pain. The same technique also showed a facilitation of transmission of painful stimuli to the cerebral cortex with shortened latency of cerebral-evoked responses to electrical oesophageal stimulation [67].

Therapeutic approaches to central sensitization

Using this model of central sensitization, the Manchester group has shown that giving prostaglandin E_2 receptor 1 (EP1) antagonists [68] and the N-methyl-D-aspartate antagonist, ketamine [69] during acid infusion can prevent central sensitization. Acid infusion up-regulates vanilloid receptor 1 expression and may induce local inflammation. The effect of EP1 antagonists therefore may be either at the tissue or spinal level. Ketamine most likely acts at the spinal level, where it blocks the excitatory amino acid receptors that mediate the facilitation of synaptic transmission seen during wind-up. The beneficial effect of ketamine also could be observed when it was given after sensitization had already occurred, suggesting that if more specific drugs could be developed without undue sedative effects, they might be viable therapeutic agents in IBS.

Modifying central nervous system pain processing

A characteristic feature of IBS patients is their vigilance toward gut symptoms. The frequently observed visceral hypersensitivity appears to have two components [70], a response bias together with an increased ability to detect gut stimulation. The response bias means that they describe as painful, sensations others would rate as discomfort. Thus they appear to have an exaggerated emotional response to gut stimuli, which psychological therapies logically would be expected to reduce.

Relaxation therapy and cognitive–behavioral therapy

Patients with IBS often score highly on scores of anxiety [71] and show enhanced measures of autonomic activation such as skin conductivity, heart rate, and heart rate variability [72]. Relaxation therapy and cognitive–behavioral therapy aim to reduce this autonomic activation without resort to drugs. Initial uncontrolled studies looked promising [73–76], but later studies suggested that although patients did well, with two thirds improving, this effect appears nonspecific and was seen equally with an attention–placebo control treatment [73,77,78]. Interpretation of many of these studies is difficult because of methodological flaws with too small numbers, lack of uniform criteria for enrollment, inadequate blinding, and use of unvalidated outcome measures [79]. A recent study, which attempted to address these deficiencies, randomized 105 patients to routine clinical care (RCC) involving 3 $\times$ 15-minute consultations with dietary and general advice plus a fiber supplement. This was compared with RCC plus either relaxation training (8 $\times$ 30-minute instructional sessions plus practice at home) or cognitive–behavioral therapy. Although there were small improvements in symptoms, there was no difference between the three groups, suggesting that any benefit was a nonspecific response to general care and attention [78]. A RCT from Germany that used a very intensive program of 10 $\times$ 60-minutes of multi-component treatment, individually tailored to the subject, gave a more positive result. Treatment included the development of a plausible illness model, educating the patient about bowel function, teaching the patient how to identify irrational beliefs, and teaching relaxation and social skills training. Although the numbers were small (12 per group), they found a significant benefit for IBS symptoms, which persisted for 6 months [80]. Overall, psychological treatments for those who are not psychologically distressed have been of limited specific value. One problem may be the difficulty in getting people to actually perform such time-consuming treatments at home. This overall negative assessment should not detract from the value of general care, however, because there is evidence that good patient–doctor interaction and adequate explanation can do a lot to improve the patient's attitude to his or her symptoms [81] and reduce subsequent health care use [82,83].

Psychotherapy

The previous studies were careful to exclude patients with overt psychological disorders. These, however, are common in IBS patients who often have anxiety and depression [84–89]. Furthermore, the IBS symptoms often develop after the onset of psychological symptoms [85], suggesting a causal role. As already indicated, major life stresses such as divorce, bereavement, and unemployment often precede consultation [90], and symptoms tend not to remit unless these chronic stressors also improve [91]. It is logical therefore to consider psychotherapy in such patients who have overt psychological disorders. One of the earliest studies enrolled 101 patients to compare 10 × 1-hour psychotherapy sessions over 3 months with conventional medical therapy and showed a convincing benefit, which persisted for at least 1 year [92]. One major problem with such a trial is choosing an appropriate control treatment, which should include non-specific attention factors that can lead to considerable improvement on their own. Another large trial (n = 102) compared psychotherapy involving an initial 2-hour assessment session followed by 6 × 45-minute psychotherapy sessions with a control group that had an initial and final assessment visit together with three short visits during which stool charts were reviewed. The patients were typical tertiary referral patients, 30% of whom had major depression and 18% anxiety states. Psychotherapy produced a clear benefit compared with control, effects which increased over the 12 months of follow-up [93]. The best predictor of improvement was the presence of anxiety and depression and the recognition by the patient that symptoms were worsened by stress. Others have found constant pain and a long previous history all predicted a poor response. This benefit suggests that the appropriate control is in fact the much cheaper standard course of antidepressants rather than standard medical care. The authors then undertook a three-way RCT of paroxetine versus psychotherapy and treatment as usual (TAU) [94]. They again confirmed the superiority of psychological therapy over TAU at 3 months, but by 15 months there were no differences between any of the three groups. There was no difference between psychotherapy and paroxetine in effectiveness as regards both abdominal pain and psychological symptoms at 3 months. The cost analysis showed psychotherapy to be initially more expensive, but because it reduced outpatient visits over the next year, it proved cheaper than standard care. Although the costs were numerically less than with paroxetine, these differences were not significant. There are some reports that psychotherapy might produce very long-lasting changes, as several studies have reported 1- to 4-year follow-ups suggesting ongoing benefit [74,95]. Thus, its cost effectiveness over an even longer time span might be even better, although this remains to be proven. These studies strongly support the use to psychological treatments for patients with overt psychological disorders, especially those who accept that their symptoms are exacerbated by stress.

What, however, of the more common, less overtly psychologically affected patient?

Antidepressants/anxiolytics therapy

As indicated previously, psychotherapy is expensive, at least initially, and not always readily available. Antidepressants, particularly tricyclics, have been used widely, and a recent meta-analysis suggests that they are among the most effective of agents with a number needed to treat of 3.2 (95% confidence interval [CI], 2.1 to 6.5) [96]. Enthusiasm should be qualified, however, because the available trials are of dubious quality [97]. The largest recent study, which used 150 mg desimipramine, reported that the drug was tolerated poorly, and only 16% actually took the full dose. Those who took the drug did improve more than placebo, but on an intention-to-treat analysis, the active arm was no better than placebo [98]. This intolerance of tricyclic adverse effects in IBS limits their use. Most practitioners use lower doses, which are subtherapeutic for depression [99,100], typically around 50 mg of tricyclic per day or less. One of the most recent RCTs used 25 mg amitriptyline, increasing to 75 mg at night and found a global improvement in 64% of patients compared with 26% in the placebo group [101]. Interestingly at this dose there was no correlation with prior depression or anxiety scores.

Long-term effects of antidepressants

There is interest in the long-term effects of antidepressants. Initially, their delayed response was attributed to the need for down-regulation of inhibitory autoreceptors, but it now is recognized that antidepressants increase the transcription factor cyclic AMP response element binding protein, which controls the production of growth factors such as brain derived nerve growth factor (BDNF) [102]. BDNF is reduced in stressed animals, something that may contribute to the atrophy of brain areas like the hippocampus, which are vulnerable to the effects of chronic stress. Antidepressants increase BDNF production in people [103] and hence antagonize the effect of stress, leading to recovery of structure and function in the hippocampus. This may explain the need for prolonged treatment and the possibility that antidepressants will induce long lasting changes in the brain, which will translate into long-term cures.

Short-term effects

Other actions, which appear much sooner, may include their mild sedative effects, which help with sleep disturbance often seen in depressed patients with IBS [104], together with their analgesic effects. These have been demonstrated in a range of chronic pain disorders such as back ache [105],

headache, fibromyalgia, and neuralgia [106]. Extensive animal studies have indicated that tricyclics have analgesic effects that act by means of opiate and adrenergic mechanisms [107], possibly by enhancing descending antinociceptive pathways. One study in diabetic neuropathy suggested tricyclics were more effective analgesics than selective serotonin reuptake inhibitors (SSRIs) [108]. More recent studies in somatic pain, however, suggest that they are equally effective with fewer adverse effects [109,110], although there is no evidence that they alter visceral pain sensitivity [111].

There are only two published RCTs of SSRIs in IBS. The first study (already discussed) used severe tertiary care IBS patients, half of whom had a psychiatric disorder [94]. The second used relatively unselected IBS patients, excluding those with a history of bipolar disorder [112]. The first study compared treatment as usual (TAU) against either psychotherapy or paroxetine 20 mg daily. Only 50% of SSRI-treated patients took the treatment, mostly because of adverse effects or unwillingness to take the drugs, while 69% randomized to psychotherapy accepted treatment. There was no significant difference in pain scores between the three groups after 3 months, but there was significantly greater improvement in quality of life with both active treatments compared with treatment as usual (TAU) as assessed by the SF36 physical component score, which persisted up to the 1-year assessment. The global improvement at 3 months was 60% (psychotherapy), 66% (paroxetine), and 38% (TAU) respectively, but this difference was no longer significant at 12 months (62%, 57%, and 51%, respectively). The second study likewise found no difference between placebo and paroxetine as regards abdominal pain but found a substantial difference in global well-being (63% versus 26%) after 12 weeks treatment [112]. Thus SSRIs are able to improve general well-being but do not appear to specifically improve bowel function, suggesting that their mode of action is largely centrally-mediated, altering the emotional response to symptoms.

Hypnotherapy

Gut-directed hypnotherapy has been used to induce a sense of relaxation and also to generate abdominal analgesia. Most of the work in IBS has come from one unit that performed the first RCT study in which 30 patients with severe refractory IBS randomly were allocated to treatment with either hypnotherapy or psychotherapy (discussion of symptoms and stress) and placebo. Hypnotherapy was associated with a small but significant improvement in abdominal pain, abdominal distension, and general well-being, but bowel habit was unchanged [113]. As one might expect from a technique that the patient can continue to use after treatment sessions have ceased, the benefit was long-lasting [114]. Older patients and those with serious psychopathology responded less well [113,114]. Over 250 patients have been treated at this single unit, and a recent audit reported improvement in bowel symptoms, quality of life, and anxiety and depression. Males

with diarrhea did worse, but other features such as anxiety levels did not predict outcome [115]. In spite of these results, the fact that no other unit has replicated the findings makes it impossible to know how well it would perform elsewhere. Objections to its cost may be false, because, although initially costly, its long-lasting effect [116] is likely to make it cost-effective over the long-term.

Summary

Irritable bowel syndrome can remit spontaneously, implying cure is possible. Predictors of good prognosis include a short history, acute onset (possibly postinfective origin), absence of psychological disorders, and resolution of chronic life stressors. Possible-disease modifying treatments with long-lasting effects include diet and anti-inflammatory and psychological treatments. Dietary modifications, which often involve excluding dairy and wheat products, are successful in some patients. Anti-inflammatory treatments have been subjected to one RCT in postinfective IBS without benefit. Probiotics may have benefit in altering bacterial flora and as anti-inflammatory agents, but further trials are needed before they can be recommended.

Psychological treatments may produce long-lasting responses. Relaxation therapy appears to have a nonspecific benefit. Psychotherapy has been shown to have long-term benefit and is particularly acceptable to, and effective for, those with overt psychological distress. Hypnotherapy has been shown to be effective in randomized placebo controlled trials and has a sustained effect.

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