

## Seminar

## Irritable bowel syndrome: a little understood organic bowel disease?

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**Irritable bowel syndrome affects 10% of adults with an unexplained female predominance. Although only a few people see their family doctor, the disease causes reduced quality of life and represents a multi-billion pound health-care problem. The disorder clusters in families, which is possibly because of intra-familial learning and a genetic predisposition. Visceral hypersensitivity is a key feature in most patients. Results of imaging studies of regional cerebral blood flow during rectal distension suggest underlying disturbances of central processing of afferent signals, though this is not unique to the disorder, since it is seen in other chronic pain syndromes. Environmental factors that are strongly implicated in at least some patients include gastrointestinal infection and inflammation and chronic stress. Diagnosis is based on positive symptoms and absence of any alarm indicators. Treatment remains unsatisfactory and hinges on an excellent doctor-patient relationship, with drugs for symptom exacerbations. Cognitive behavioural treatment, psychotherapy, and hypnosis could provide long-lasting benefit in some patients. Tricyclic antidepressants in low doses seem to be the most effective class of drugs for the disorder on the basis of limited data.**

Irritable bowel syndrome is a frequent yet little understood disorder. Patients present to family doctors, gynaecologists, surgeons, and gastroenterologists with abdominal pain or discomfort and an erratic bowel habit; they frequently undergo extensive testing before a diagnosis is reached. The disorder substantially impairs quality of life, and overall health-care costs are high. Irritable bowel syndrome has therefore gained increased attention from clinicians, researchers, payers, and industry.

Relegated in the past to the realm of the psychosomatic and unimportant, research is now beginning to define the mechanisms of this heterogeneous disorder. Genetics, infection, mucosal inflammation, and disturbed central processing of abnormal sensory afferent signals all play a part, their importance varying from one patient to another. These insights could lead to new diagnostic approaches and therapeutic targets. We aim here to review published work, focusing on approaches to diagnosis and management on the basis of relevant pathophysiological insights.

### New definitions: confusion and consensus

The term irritable bowel was probably first coined in 1944 by Peters and Bagen.<sup>1</sup> Irritable bowel syndrome was deemed a diagnosis of exclusion until Heaton's research group in Bristol reported that six symptoms could discriminate people diagnosed with the disorder (based on an absence of organic disease on follow-up) from those with documented structural bowel disease (panel 1). Presence of two or three symptoms, referred

to as the Manning criteria,<sup>2</sup> were subsequently applied in many epidemiological and clinical studies to identify irritable bowel syndrome, but investigators disagreed on their use. Although researchers have shown that the more of these symptoms that are present, the higher the probability of a diagnosis of irritable bowel syndrome, their validity in men for example seem poor.<sup>4</sup>

In an attempt to bring order to the specialty, a consensus-based approach was adopted by a group of international experts,<sup>3</sup> which led to development of the Rome criteria for irritable bowel syndrome. Although many individuals fulfil the Manning but not the Rome criteria for the disorder,<sup>5,6</sup> nonetheless, the Rome consensus has resulted clearly in a standardisation of entry criteria into clinical studies, allowing investigators to compare their results with confidence.

Some sex differences, in terms of symptom expression in irritable bowel syndrome, have been recorded, with more women than men reporting the disorder, although symptom severity, illness effect, and psychological distress levels seem to be similar in men and women.<sup>7</sup> Constipation, distension, mucus, and nausea are more frequent in women than men,<sup>4</sup> and symptoms seem to be linked to the menstrual cycle in some studies,<sup>8</sup> although this finding is controversial.<sup>7</sup> More women with irritable bowel syndrome report having had a hysterectomy than those without this disorder,<sup>9</sup> which could indicate misdiagnosis of pelvic pain or an overlap of the disorder with pelvic pathology.

Some evidence suggests that inclusion of absence of alarm indicators with Rome criteria (panel 2) increases

### Search strategy and selection criteria

A comprehensive Medline search was done with the MeSH terms "irritable bowel syndrome" and "functional bowel disease" from 1997 until February, 2002. Only articles published in English were retrieved. Furthermore, a hand search of abstracts published in *Gastroenterology* on irritable bowel syndrome over the past 4 years was undertaken, but only those that provided important insights or had high further-reading value have been cited.

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**Panel 1: Criteria for irritable bowel syndrome****Manning criteria (1978)\***

- Pain relieved by defecation
- Looser stools at pain onset
- More frequent stools at pain onset
- Visible abdominal distension
- Passage of mucus
- Feeling of incomplete rectal emptying

**Rome II criteria (1999)<sup>‡</sup>**

- Pain or discomfort for 12 weeks of the previous 12 months associated with two of the following three:
- Relief with defecation
  - Looser or more frequent stools
  - Harder or less frequent stools
- Symptoms that cumulatively lend support to the diagnosis:
- Abnormal stool frequency (>3 bowel movements per day and <3 bowel movements per week)
  - Abnormal stool form (lumpy/hard or loose/watery)
  - Abnormal stool passage (straining, urgency, or feeling of incomplete rectal emptying)
  - Passage of mucus
  - Bloating or feeling of abnormal distension

\*Various cutoffs were applied in subsequent clinical and epidemiological studies—eg, more than two symptoms plus abdominal pain. †Alarm features and psychological measures are not part of the criteria.

diagnostic certainty, with one report showing 100% specificity for irritable bowel syndrome, although sensitivity was substantially lower.<sup>10</sup>

**Epidemiology**

Gastrointestinal symptoms are strikingly frequent in the general population: 60–70% of people report one or more troublesome symptoms, suggesting that to be completely asymptomatic could be abnormal.<sup>11</sup> Irritable bowel syndrome is clearly one of the most frequent explanations for chronic symptoms, although true prevalence varies—depending on criteria used—from 3% to 22%.<sup>6,11,12</sup> Prevalence of this disorder is only slightly reduced in elderly people, in whom it is often misdiagnosed. Irrespective of the definition applied, irritable bowel syndrome has a substantial effect on quality of life<sup>13,14</sup> and health-care costs.<sup>13,15</sup>

Present controversy is whether irritable bowel syndrome, functional dyspepsia, chronic fatigue, fibromyalgia, and other unexplained chronic symptoms represent a manifestation of one functional somatic syndrome, akin to somatisation disorder, or whether

**Panel 2: Alarm indicators that suggest organic disease is more likely than irritable bowel disease**

- Age of onset older than 50 years
- Progressive or very severe or non-fluctuating symptoms
- Nocturnal symptoms (eg, diarrhoea, pain) waking the patient from sleep
- Persistent daily diarrhoea
- Rectal bleeding or evidence of anaemia
- Unexplained weight loss
- Recurrent vomiting
- Positive family history of colon cancer
- Fever
- Abnormal physical examination (apart from mild abdominal tenderness), eg, skin rash, anaemia, mouth ulcers, rectal mass, pain on tensing abdominal wall muscles

irritable bowel syndrome is a distinct entity.<sup>16</sup> Only development of molecular or other disease markers will resolve this dispute, but there is indirect evidence suggesting that the disorder represents a distinct symptom grouping.<sup>17,18</sup> Results of population-based studies<sup>17,18</sup> applying factor analysis (a statistical technique that identifies independent groupings of symptoms) and cluster analysis (that identifies independent groupings of individuals) have shown that a frequent entity that accords with irritable bowel syndrome arises similarly in different countries. However, the overlap in terms of sex (female predominance), psychological associations, and response to antidepressant and psychological treatment among the functional somatic disorders is as yet unexplained.

The natural history of irritable bowel syndrome is surprisingly poorly defined. Prevalence is stable because onset of symptoms is balanced by disappearance in the community.<sup>19,20</sup> Symptoms typically fluctuate: Hahn and colleagues<sup>21</sup> showed that over 12 weeks, symptoms arose a mean of 12 times with maximum duration of 5 days, affecting patients on about 50% of days. Long-term follow-up studies are sparse, but irritable bowel syndrome has a good prognosis and, at least in a few individuals, symptoms can resolve.<sup>19,22</sup>

Observations suggest that low-density childhood living conditions predispose to irritable bowel syndrome (with over a three-fold increased risk).<sup>23</sup> We postulate that this finding could indicate less exposure to multiple infections in childhood and development of a protective T helper 2 immune response. Antibiotic use might be a risk factor, but could reflect the link with gastroenteritis as discussed below,<sup>23</sup> and the association is controversial.

**Health care-seeking behaviour**

Not all people with irritable bowel syndrome present for medical care—the proportion who do varies greatly between countries.<sup>11,24,25</sup> Much of the variation in rates of health care-seeking behaviour is probably attributable to characteristics associated with a country or region's health-care system (including access and who pays).

Social learning in early childhood could contribute to frequent seeking of health care for symptoms of irritable bowel syndrome. Levy<sup>26</sup> reported that children whose parents have the disorder consulted outpatient services for gastrointestinal symptoms and general health concerns more often than matched controls who did not have the disorder.

Psychological distress is thought to be a major factor in use of health care by adults with irritable bowel syndrome, but evidence is conflicting.<sup>25</sup> Outpatients with this disorder have high levels of psychopathology (in particular, generalised anxiety, depression, and hypochondriasis),<sup>4,27,28</sup> but these findings could be the result of selection bias, since distressed people are most likely to be referred to specialist centres. In volunteer studies, researchers reported that people who did not seek health care for irritable bowel syndrome had a psychological profile similar to that of controls without the disorder, leading to the conclusion that psychological factors drive seeking of health care but are not of causal importance in irritable bowel syndrome.<sup>4,29</sup> Results of other studies<sup>27,30</sup> do not accord with these findings. A comprehensive understanding of factors that explain why people with irritable bowel syndrome seek health care is thus unavailable, but symptom severity, especially pain, and duration of illness have some role.<sup>25,27,30</sup>

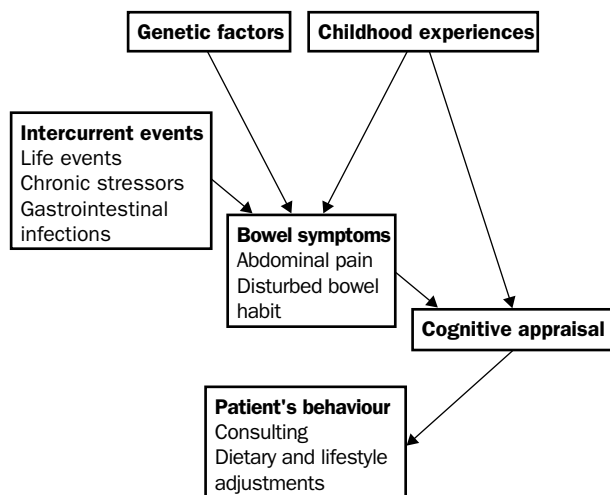


Figure 1: Hypothetical relation between putative predisposing genetic and psychological factors and subsequent development of irritable bowel syndrome

## Pathophysiology

### Mechanisms

The symptoms of irritable bowel syndrome are pain, bloating, and an altered bowel habit. Putative mechanisms include visceral hypersensitivity, altered motility, abnormal transit of stool and gas, and stress, more than one of which could contribute to symptoms, which after cognitive appraisal lead to patient's behaviour, including consultation (figure 1). Genetic factors affecting pain-signalling and disturbances in central processing of afferents are postulated to predispose to irritable bowel syndrome after specific environmental exposures.

### Role of stress

Although most patients with irritable bowel syndrome agree that stress aggravates the disorder,<sup>31</sup> variance in bowel symptoms attributable to acute stress is only 11%.<sup>32</sup> Decisive interventional studies are difficult to do in human beings owing to ethical constraints. Moderately severe stresses in rats release corticotropin-releasing factor, delaying gastric emptying and accelerating colonic transit.<sup>33</sup> Patients with irritable bowel syndrome show an exaggerated colonic response to infusions of corticotropin-releasing factor,<sup>34</sup> as they do to several other drugs.<sup>35</sup>

Chronic sustained stressors such as separation and bereavement are probably more important than acute stressors in establishment of onset<sup>36</sup> and persistence of symptoms in patients with irritable bowel syndrome.<sup>37</sup> In rodents, maternal separation in the perinatal period, which induces an anxiety state, causes visceral hypersensitivity, suggesting that childhood stress could be relevant to symptoms of the disorder.<sup>38,39</sup>

### The idea of visceral hypersensitivity

Patients with irritable bowel syndrome were first shown to be hypersensitive to rectal balloon distension 30 years ago.<sup>40</sup> This occurrence becomes increasingly complex the more it is studied. First, visceral hypersensitivity is reported in only about 60% of patients.<sup>41</sup> Second, anticipation has an important role. When distension is done with a steadily ascending magnitude, patients have a lower pain threshold than controls, whereas if the

same volumes are presented in random order, then mean thresholds are similar.<sup>42</sup> This decreased threshold is partly attributable to so-called hypervigilance or excessive attention to, or fear of, painful stimuli from the gut, and partly due to so-called true hypersensitivity, indicating an enhanced detection of visceral stimuli.<sup>42</sup> Even individuals with normal sensitivity develop hypersensitivity after repeated distension of the colon, which is not seen in controls.<sup>43</sup> This sensitisation could happen either within the dorsal horn of the spinal cord, in which visceral and somatic nerves converge on one second-order afferent neurone, or in the central nervous system. Enhanced excitability of this pathway results in increased viscerosomatic referral, such that pain attributable to visceral distension is seen over more dermatomes than normal.<sup>41,44</sup>

### Abnormal brain activation in irritable bowel syndrome

Functional imaging in irritable bowel syndrome, including positron emission tomography and functional MRI, shows a greater than normal increased blood flow in the anterior cingulate cortex during anticipation and actual colonic stimulation.<sup>45,46</sup> Anticipation and experience of a range of painful stimuli—visceral (including oesophageal,<sup>47</sup> gastric distension,<sup>48</sup> and angina pectoris)<sup>49</sup> and somatic (eg, subcutaneous alcohol injection)<sup>50</sup>—activate closely related but distinct areas of the anterior cingulate cortex. Degree of activation is proportional to negative feelings induced by such stimuli.<sup>51</sup> Activation happens during anticipation of an unpredictable noxious stimulus, whereas deactivation (a fall in blood flow) can be seen before a predictable noxious stimulus. This occurrence could represent an attempt to keep pain to a minimum by deliberate distraction (thinking about something else),<sup>52</sup> which patients with irritable bowel syndrome seem less able to do than those without. Such findings are not unique to this disorder, since similar results have been reported in patients with atypical facial pain.<sup>53</sup>

The brain is not only important for interpretation of stimuli and relation of them to previous memories, but it also has an important effect on ascending pain signals. The descending antinociceptive system, which inhibits transmission of pain, could be defective in irritable bowel syndrome and other chronic painful disorders such as fibromyalgia.<sup>54,55</sup> Antidepressants, which are one of the most effective treatments for pain in irritable bowel syndrome, could act by enhancement of these descending antinociceptive effects.

### Altered colonic motility

Dependent on precise definitions used, patients with irritable bowel syndrome can be divided by bowel habits into three groups of roughly equal size: those with predominantly loose or frequent stools, those with predominantly hard or infrequent stools, and those with variable or normal stools, all presumably secondary—at least in part—to disturbed motor function.<sup>56</sup>

**Exaggerated response to eating**—More than 50% of patients with irritable bowel syndrome report exacerbation of symptoms after eating, and this occurrence can be objectively shown.<sup>57</sup> Eating is, of course, a major stimulus to colonic motility; outcomes of this stimulation depend on the balance between mixing of motor patterns, which predominates in healthy people,<sup>58</sup> and propulsive contractions, which seem to be exaggerated in diarrhoea-predominant irritable bowel syndrome.<sup>59</sup>

Many researchers have reported that patients with this form of the disorder have increased sensitivity to cholecystokinin and an exaggerated response to eating.<sup>39,59</sup> Furthermore, a cholecystokinin-1 antagonist, loxiglumide, selectively slowed proximal colonic transit in patients with this disorder but not in controls,<sup>60</sup> although this drug class might relieve constipation. By contrast, patients with constipation-predominant irritable bowel syndrome have fewer propulsive contractions after eating.<sup>61</sup> Patients with diarrhoea-predominant irritable bowel syndrome have shorter small-bowel and colonic transits than those with constipation.<sup>62</sup> Those in whom bloating is a main symptom have accelerated rather than slow small-bowel transit.<sup>63</sup>

**Evidence of abnormal gas propulsion and expulsion—**Bloating is a very frequent symptom in the normal population and in people with irritable bowel syndrome. An ambulatory technique for measurement of girth<sup>64</sup> has shown that abdominal girth normally increases during the day, peaks in the late evening, and diminishes rapidly on adoption of the supine posture. Distension does not seem to be caused by weak abdominal muscles or impaired activation of these muscles on changing of posture.<sup>65</sup> It could, in some individuals, be due to abnormal colonic fermentation with excessive hydrogen production,<sup>66</sup> which could explain the response of patients to exclusion of poorly absorbed carbohydrate.<sup>67</sup> Although results of studies have not shown evidence of increased gas production in patients with irritable bowel syndrome, signs of abnormal propulsion of gas through the gut have been noted in some individuals with this disorder.<sup>68</sup>

Distension by infusion of gas into the small intestine only induces bloating and abdominal discomfort in healthy volunteers if they do not pass it rapidly through the gut.<sup>69</sup> This retention of gas is much more frequent in irritable bowel syndrome than in health.<sup>69</sup> Serra and colleagues<sup>70</sup> reported that discomfort induced by gas infusion was much greater when normal volunteers were asked to voluntarily refrain from passing flatus per rectum than when they were allowed to pass it freely. Whether social inhibitions on passing flatus are most striking in people with irritable bowel syndrome has not been studied, but this factor might explain some of their discomfort.

Colonic transit is usually within the normal range in irritable bowel syndrome,<sup>63</sup> but results of reports suggest that pelvic-floor dysfunction could be a feature in some patients with this disorder.<sup>71,72</sup>

#### Role of dietary intolerance

Maldigestion, excessive gas, and abnormal transit can all underlie intolerance of specific foods, which many patients with irritable bowel syndrome believe contribute to their symptoms. Exclusion diets are difficult for the patient, and although up to 40% of patients can respond,<sup>67</sup> most clinicians do not see such good results. The most frequently implicated foods in these diets are wheat and milk.

**Lactose intolerance—**This intolerance is a genetic trait reported in 10% of the northern European population, increasing to 40–60% in Asians, 60–80% in Africans, and 90% in Chinese patients.<sup>73</sup> Since symptoms are closely similar to those of irritable bowel syndrome, a dietary history of lactose ingestion is useful. Evidence of lactose intolerance in response to a 50 g load of lactose is not necessarily relevant unless the individual habitually consumes substantial amounts of lactose.<sup>74</sup> Many people do not ingest more than 12.5 g of lactose a day, which is

typically the minimum needed to induce symptoms—since, in acquired hypolactasia, a residual ability to digest small amounts of lactose is usually present.

**Wheat intolerance or allergy?—**Most people from Europe and the USA eat substantial amounts of wheat, often several hundred grams per day, 10–15% of which is in a form that cannot be digested by human enzymes.<sup>75,76</sup> Although fermentation of this malabsorbed fraction in the colon can account for some intestinal symptoms, patients showing signs of irritable bowel syndrome might have a subtle form of gluten intolerance characterised by normal villi but increased intraepithelial lymphocytes.<sup>77</sup> A subset of patients who have the coeliac-associated human leucocyte antigen genotype DQ2 might respond to a gluten-free diet.<sup>77</sup> Although exaggerated responses to food antigens injected into the skin are frequent, without other manifestations of allergy, such as urticaria and angioneurotic oedema, these are not clearly linked to symptoms on double-blind food challenge.<sup>78</sup>

#### Role of inflammation

Normal intestine is in a chronic state of inflammation, with a balance between commensal enteric organisms and the immune system. Although colonic biopsy specimens are normal in patients with this disorder, in those who have also had a bout of *Campylobacter enteritis*, an increase in rectal mucosal lymphocytes has been reported.<sup>79,80</sup> Small-bowel permeability has also been shown to be greatly increased,<sup>79</sup> but these findings need replication in other centres.

Inflammation is associated with production of mediators including prostaglandins, bradykinins, nerve growth factors, adenosine, and 5-hydroxytryptamine. These mediators induce visceral hypersensitivity, exaggerated motor responses, and increased intestinal secretions<sup>81</sup> (figure 2), which could contribute to episodic diarrhoea. Inflammation also increases availability of 5-hydroxytryptamine by raising enteroendocrine cell counts, which could also contribute to diarrhoea. Serotonin type 3 (5HT<sub>3</sub>) antagonists are effective at reduction of symptoms in diarrhoea-predominant irritable bowel syndrome. However, these findings might not necessarily be

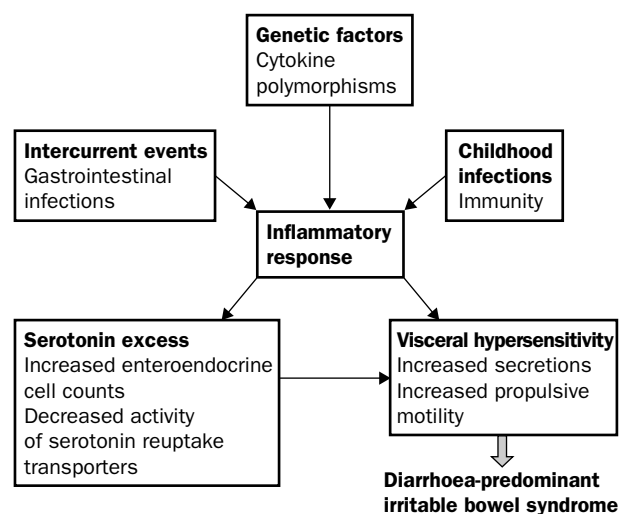


Figure 2: Possible mechanisms accounting for post-infective irritable bowel syndrome

causally linked, and intervention studies are needed to establish whether inhibition of inflammation induces any clinical benefit.

5-hydroxytryptamine has an important role in the peristaltic reflex, because it is released by pressure or stroking from enteroendocrine cells and then it acts on primary intrinsic afferent neurones to initiate ascending excitation and descending inhibition.<sup>82</sup> A 5HT<sub>3</sub> antagonist, alosetron, delays transit, relaxes the colon, and improves symptoms of diarrhoea-predominant irritable bowel syndrome.<sup>83</sup> Furthermore, the partial serotonin type 4 (5HT<sub>4</sub>) agonist tegaserod accelerates small bowel and right colonic transit, softens stools, and modestly improves symptoms of constipation-predominant irritable bowel syndrome.<sup>84</sup> Houghton and colleagues<sup>85</sup> reported that some patients with diarrhoea-predominant irritable bowel syndrome had exaggerated release of 5-hydroxytryptamine after a meal, which lends support to use of 5HT<sub>3</sub> antagonists; however, these data need verification.

Raised concentrations of serotonin-containing enteroendocrine cells have been reported in patients with irritable bowel syndrome after infection with campylobacter and possibly other organisms,<sup>86</sup> which could explain the increased postprandial release of 5-hydroxytryptamine and bowel symptoms in these patients. Concentrations of these cells are reduced in idiopathic slow-transit constipation in some studies<sup>87</sup> but not all.<sup>88</sup> Success of 5HT<sub>3</sub> antagonists in treatment of diarrhoea-predominant irritable bowel syndrome suggests that increased 5HT-containing enteroendocrine cells might be important in causing symptoms, though this possibility has still to be established by double-blind, randomised, placebo-controlled studies linking clinical response to enteroendocrine cell numbers.

#### *Abnormal colonic flora*

Results of studies of colonic fermentation suggest that colonic flora might be abnormal in patients with irritable bowel syndrome,<sup>67</sup> and that probiotics, which might alter flora without the disadvantages associated with antibiotic use, could have a role in treatment. Results of a randomised controlled study of lactobacillus showed a reduction in flatulence and abdominal pain;<sup>89</sup> confirmatory studies are awaited.

#### *Psychological factors*

Studies of a causal relation between irritable bowel syndrome and psychological distress show conflicting results.<sup>4,27,28,30,90</sup> Psychiatric diagnoses are substantially increased in patients with this disorder seen in referral centres,<sup>4</sup> but an association in the general population is not as great.<sup>27,91</sup>

Results of population-based and clinic-based studies have suggested that some people with irritable bowel syndrome report a history of sexual, physical, or emotional abuse,<sup>92-94</sup> although what constitutes a memory of abuse remains controversial. Mechanisms that could link abuse and irritable bowel syndrome, however, are mostly unknown. The most promising explanation is that a history of abuse is associated with another factor (eg, neuroticism), which predisposes to the disorder,<sup>90</sup> though this is controversial.<sup>94</sup>

Alternatively, researchers have suggested that patients who have been abused might have symptoms of irritable bowel syndrome because of enhanced visceral sensitivity. Some evidence suggests that outpatients with irritable bowel syndrome who have been abused report lower pain thresholds in response to finger pressure and have a greater tendency to set lower standards for judging

stimulus as noxious than do patients with this disorder who have not been abused.<sup>95</sup> However, whether or not they had been abused, women with the disorder had similar pain-thresholds during rectal distension.<sup>96</sup>

#### *Genetics versus environment*

After limited evidence that irritable bowel syndrome tends to cluster in families,<sup>97</sup> twin studies have been undertaken to ascertain if there is a genetic component. Two studies have reported that the disorder is twice as frequent in monozygotic twins compared with dizygotic twins.<sup>98,99</sup> Whether this genetic link is explained by overlap of depression or other diseases with irritable bowel syndrome is unknown. However, few studies have been done that report an increased prevalence of psychiatric disorders in relatives of patients who have this disorder.<sup>100</sup>

Although results of twin studies suggest that environmental factors affect pathogenesis more than genetic factors do, an interaction seems probable. For example, genes controlling downregulation of inflammation might be different in some patients with irritable bowel syndrome, which could account for susceptibility to the disorder after infection.<sup>101</sup>

Similarly, several congenital motility disorders have now been recognised, and the molecular basis of these is being uncovered.<sup>102,103</sup> Of possible relevance to irritable bowel syndrome, the molecular dysregulation of peristalsis has been recognised in acquired diseases, as seen in young women with very severe constipation because of idiopathic slow colonic transit.<sup>103</sup> Preliminary data suggest that neural abnormalities in the myenteric plexus might also arise in severe irritable bowel disease unaccompanied by obvious evidence of intestinal pseudo-obstruction.<sup>104</sup> Such findings make it more possible that the phenotype of irritable bowel syndrome includes a subset with molecular neural dysregulation, perhaps inherited, that could be characterised should sufficient tissue become available.

A family of neurotropic factors has been identified that could have therapeutic potential in irritable bowel syndrome. Neurotrophin-3 (NT-3), for example, has been shown to stimulate gut motility, probably caused by direct stimulation of neuromuscular nerves.<sup>105</sup> In one trial,<sup>105</sup> NT-3 did seem to be efficacious in chronic constipation, but more studies are needed.

#### **Diagnosis**

There is presently no established biological marker for irritable bowel syndrome. For example, colonic balloon distension testing is invasive and is not sensitive and specific enough to justify its clinical use. One of the main reasons that family doctors refer patients with symptoms of irritable bowel syndrome to hospital is the possibility that they might have another disease. Thus, it is not surprising that incidence of organic disease is higher in patients referred to a specialist than in those seen in primary care.<sup>106</sup>

A patient's history is important, because it affects their a priori probability of a correct diagnosis; most patients do not need tests for organic disease unless there are alarm indicators.<sup>107</sup> Age is important for a correct diagnosis of irritable bowel syndrome; patients over the age of 50 with new bowel symptoms, especially those with a family history of colon cancer, should have this cancer excluded before concluding that they have irritable bowel syndrome.

In patients younger than 50 years, knowing the amount of milk consumed will strongly affect whether a diagnosis of lactose intolerance should be pursued. However, frequency of lactose intolerance in patients with irritable bowel syndrome is similar to that in the general

population, and hence is usually not the true explanation for symptoms of the disorder.<sup>108,109</sup>

Up to 5% of patients in the UK with symptoms similar to those for irritable bowel syndrome have coeliac disease (compared with 0.5% of controls).<sup>110</sup> This disorder should be screened for with antiendomysial antibodies. A full blood count, renal and liver function tests, thyroid function testing, and investigation of stool sample for parasites all have very low yields but are inexpensive.<sup>109</sup>

Low-grade Crohn's disease is rare, but is easy to miss because erythrocyte sedimentation rate and concentrations of C-reactive protein are not always raised. Presently, diagnosis of this disorder generally cannot be made without radiological analysis of the small bowel, so missed diagnoses will probably still happen if we are to avoid unnecessary gonadal irradiation.

A SeHCAT (75-seleno-homocholic acid-taurine) test is needed to diagnose idiopathic bile-salt malabsorption, though a therapeutic trial of cholestyramine is an inexpensive and alternative way to screen for this rare disorder.<sup>111,112</sup>

Endoscopy is an expensive and limited resource, thus we should probably reserve use of it for patients with persistent diarrhoeal symptoms in whom duodenal and colonoscopic biopsy specimens might be needed to exclude coeliac disease and microscopic colitis, respectively. However, the diagnostic yield of colonic biopsy is very low.<sup>109,113</sup> A high proportion of patients do improve during follow-up, so a staged approach, though lengthy, could save resources and avoid unnecessary procedures.

Dietary and symptom diaries can identify patterns of symptoms that might be associated with food or stress. Exclusion diets have proven effective, especially in some patients with diarrhoea,<sup>67</sup> and a positive response to such a diet can bring an end to the cycle of negative tests. If constipation is severe, colonic-transit testing (to exclude slow-transit constipation) and pelvic-floor testing (to exclude outlet obstruction) could be useful to guide further management,<sup>4,71,72</sup> but yield in patients with classic symptoms of irritable bowel syndrome is not established and is likely to be low.

## Management

### *Education and support*

Authors of several consensus reports<sup>107,114,115</sup> have made management recommendations and reached similar conclusions (panel 3). After a positive diagnosis based on symptoms, education and support of patients is essential to deal with what is often a lifelong disorder. Establishment of a positive doctor-patient relationship is important to provide good clinical care, especially in view of qualitative evidence that patients with irritable bowel syndrome generally perceive their doctor to have negative medical beliefs about the disorder or themselves (neurotic) and do not provide adequate medical information or support.<sup>116,117</sup> Evidence of a good doctor-patient relationship has been associated with reduced return visits.<sup>22</sup> Education classes and patients' support groups provide valuable assistance for those with troublesome symptoms.<sup>118</sup>

### *Diet*

A high-fibre diet has been deemed the standard of care for irritable bowel syndrome, but evidence that fibre helps this disorder is at best equivocal. Wheat bran seems to be no better than placebo. In 100 consecutive

### Panel 3: Management recommendations for irritable bowel syndrome

- Make a positive diagnosis based on symptoms and absence of alarm features: many patients do not need colonic investigation
- Establish effect of illness and patient's psychosocial resources (eg, family support)
- Establish if there is a comorbid psychiatric disease or an unresolved major loss or trauma
- Provide firm reassurance, emphasising their symptoms are known to be real (not just "in their head") and that irritable bowel syndrome is a recognised bowel disease
- Provide education, including an understandable explanation of why symptoms might arise, emphasising that the patient is not alone in their suffering and the prognosis is benign
- Assess the patient's expectations and hidden fears—eg, find out why they have presented now despite longstanding symptoms—and try to address all concerns
- Avoid giving mixed messages—eg, by reassuring the patient then ordering extensive tests without an adequate explanation
- Avoid repeated tests unless new development of structural disease is suspected—eg, presentation with new alarm features
- Centre treatment on the principle of patient-based responsibility for care
- Set realistic treatment goals. Consider referral to a patients' support group
- Organise a continuing care strategy if symptoms have been chronic or disabling
- Try dietary modification first-line—eg, a low fibre diet for diarrhoea and a cautious increase in fibre for those with constipation. Avoid obvious food precipitants
- Prescribe drugs sparingly if possible, targeting the symptom of most concern to the patient and providing frequent drug holidays where feasible (with the exception of antidepressants)
- Consider psychological treatments for those with moderate-to-severe symptoms

patients with the disorder, 55% reported that bowel habit, distension, and pain were all made worse, whereas only 10% felt better on bran.<sup>119</sup> Results of meta-analyses<sup>120</sup> of available trials have concluded that fibre supplements are not shown to be superior to placebo, but could improve constipation. Fibre and fibre supplements, if prescribed, should be introduced gradually.

If abnormal colonic flora populate some patients with irritable bowel syndrome, then certain diets could precipitate colonic malfermentation and increased gas. In a crossover study<sup>67</sup> of six patients with the disorder and six controls, an exclusion diet was shown to reduce symptoms and hydrogen gas production in patients. Results of small trials<sup>89,121</sup> of probiotics suggest they might be of some benefit in treatment of patients with irritable bowel syndrome, but there are no convincing data.

### *Antispasmodics*

Abdominal pain is a major symptom of irritable bowel syndrome. Poynard and colleagues<sup>122</sup> updated a meta-analysis that included 23 randomised controlled trials. They concluded that anticholinergics and antispasmodics were superior to placebo in treatment of the disorder. However, the quality of most of the trials

#### Panel 4: Drugs presently available for irritable bowel syndrome\*

##### Established efficacy

Tricyclic antidepressants (low dose)  
Loperamide (diarrhoea)  
Alosetron (diarrhoea-predominant: withdrawn but may have limited rerelease)  
Tegaserod (constipation-predominant: released in some countries)

##### Uncertain efficacy

Anticholinergics/antispasmodics (pain)  
Selective serotonin reuptake inhibitors  
Bile-salt sequestering agents (diarrhoea)  
Osmotic and stimulant laxatives (constipation)  
Prostaglandin E analogue (misoprostil: constipation)  
Gonadotropin-releasing hormone analogues (leuprolide)  
Somatostatin analogues  
Chinese herbal medicine  
 $\alpha$ -adrenergic agonists (eg, clonidine)

##### Probably not efficacious

Cisapride, domperidone  
Anxiolytics  
Phenytoin  
 $\beta$ -blockers

\*Based on available meta-analyses of clinical trials, or large randomised double-blind studies versus placebo.

included in the meta-analysis was very poor, results were mixed, publication bias was not excluded, and if there was an effect it was undoubtedly small. Moreover, no trials have tested efficacy of sublingual anticholinergic agents (panel 4).

#### Laxatives

Typically taken by people with constipation, the value of this class of drugs is uncertain.<sup>5</sup> Osmotic laxatives frequently induce worse bloating and pain, although polyethylene glycol preparations could be better. However, there are few randomised trials of laxatives in treatment of irritable bowel syndrome. Stimulant laxatives are probably safer than has been previously appreciated, but since they usually induce abdominal cramps, they seem unsatisfactory for treatment.

#### Antidiarrhoeals

Opioids are effective for treatment of diarrhoea but not for pain.<sup>120</sup> Loperamide is most frequently studied and is advantageous because it does not have central side-effects. Opioids are best prescribed intermittently, but rebound constipation restricts their use in irritable bowel syndrome. Bile-salt sequestering drugs are worth a try in resistant patients with this disorder, but there are few randomised controlled trials.<sup>112</sup> Other antidiarrhoeals, including bismuth compounds, are of unknown value.

#### Antidepressants

Tricyclic antidepressants, on the basis of one meta-analysis,<sup>123</sup> represent the most effective drugs for treatment of irritable bowel syndrome, with a number needed to treat of three. However, the quality of trials has been questioned (partly because of small sample sizes and short duration), and side-effects do limit use in practice<sup>120,124</sup> (panel 5). Selective serotonin reuptake inhibitors have been said to be useful in irritable bowel syndrome but supportive evidence is very limited.<sup>125</sup>

#### Panel 5: Novel therapies under consideration for irritable bowel syndrome

	Drug	Findings
<b>Serotonergic modulators</b>		
5HT <sub>4</sub> agonist	Tegaserod	Effective in constipation-predominant irritable bowel syndrome in large trials
5HT <sub>4</sub> antagonist	Piposered	Slowed transit in one small trial. Yet to be fully assessed
5HT <sub>3</sub> antagonist	Alosetron	Effective in large trials in diarrhoea-predominant irritable bowel syndrome but withdrawn owing to side-effects
	Cilansetron	Presently under assessment
<b>Opioids</b>		
Kappa agonists	Fedotozine	Marginal efficacy in irritable bowel syndrome in large studies
	Asimadoline	Evidence of benefit limited
	Trimebutine	Evidence of benefit limited
<b>Other agents</b>		
Corticotrophin-1 antagonist	NBI 34041	Presently under assessment
Neurokinin 2 receptor antagonist	Saredutant	
Cholecysto-kinin-1 antagonists	Dexloxi-glumide	Effective in constipation-predominant irritable bowel syndrome and large trials pending

#### Serotonin receptor agonists and antagonists

In clinical trials, alosetron was shown to be an efficacious drug in irritable bowel syndrome, which improved global symptoms, diarrhoea, and quality of life, but not bloating in women.<sup>83,126,127</sup> However, an unacceptable side-effect profile (ischaemic colitis and severe constipation) led to its withdrawal in 2000 by the manufacturer,<sup>128</sup> although it may be rereleased. Other 5HT<sub>3</sub> antagonists are available (eg, ondansetron) but have uncertain efficacy in diarrhoea-predominant irritable bowel syndrome; cilansetron is in clinical trials.<sup>128</sup>

Tegaserod is a partial 5HT<sub>4</sub> agonist that is a prokinetic drug.<sup>128,129</sup> It has modest efficacy in constipation-predominant irritable bowel syndrome but should be regarded as a second-line agent after diet and laxatives have failed until head-to-head trials with first-line therapy are available.<sup>84,129</sup> Other 5HT<sub>4</sub> agonists are being tested.<sup>128</sup>

#### New and alternative treatments

Several compounds are under development or in early testing for irritable bowel treatment (panel 5). It remains to be seen if pharmacogenetics or other means of subgrouping the disorder will lead to drug advances.

Psychological treatments are thought to be of value in irritable bowel syndrome. Cognitive behavioural therapy, relaxation, and psychotherapy have been reported to be superior to standard care in most patients,<sup>130-133</sup> but methodological concerns have been raised with most of the trials.<sup>134</sup> Hypnotherapy has been arguably the most promising treatment in randomised trials,<sup>134</sup> with benefit continuing even after 12 months.<sup>135,136</sup> However, it should be noted that patients with overt psychiatric disease do not do well with this mode of therapy.<sup>135</sup> Biofeedback seems useful for severe constipation and can improve pelvic-floor function and colonic transit, but randomised controlled trials are few in adults.<sup>137</sup> There is increasing interest in multimodal treatment, combining psychological therapy with antidepressants, and trials are in progress.

Many patients with irritable bowel syndrome seek alternative care. In a high quality trial, Chinese herbal medicine (combining 20 herbs) was, rather surprisingly, superior to placebo, but this finding needs replication.<sup>138</sup> On the other hand, in a double-blind controlled study,<sup>139</sup> acupuncture was of no therapeutic benefit for the disorder, and reflexology failed in a small single-blind trial.<sup>140</sup>

## Conclusions

Irritable bowel syndrome is a major cause of morbidity and deserves serious attention. Although stress can stimulate the colon in this disorder and in health, this factor cannot be the only cause of symptoms. Evidence is growing that irritable bowel syndrome can no longer be purely regarded as a functional disorder—which is a loose term frequently used to describe anything that we cannot adequately explain, or probable psychiatric disease. We prefer to judge the disorder to be a discrete collection of organic bowel diseases, with characteristic morphological, psychological, and physiological changes now only being fully appreciated. We believe that such a view will benefit research in the area, and eventually our patients.

### Conflict of interest statement

N J Talley has been a consultant for Novartis, Forest, GlaxoSmithKline, AstraZeneca, Takeda, and Procter and Gamble. R Spiller has been a consultant for GlaxoSmithKline, Novartis, and Procter and Gamble, and his department has received educational grants from AstraZeneca and Novartis.

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