Fortnightly Review

Irritable bowel, irritable body, or irritable brain?

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The irritable bowel syndrome is probably the most common disorder encountered by gastroenterologists in the industrialised world and the most common functional bowel disorder seen by physicians in primary care. Most people with symptoms of the condition (60-75%) do not consult a doctor. The cause of the irritable bowel syndrome is unknown, its development is poorly understood, and perhaps not surprisingly no universally agreed approach to treatment exists. Indeed it has been argued that controlled clinical trials have failed to show that any drug is effective in this condition. The irritable bowel syndrome is therefore a challenge for both doctors and patients, and important advances in treatment will probably not occur until the cause and development are better understood.

The irritable bowel syndrome, the most common of the functional bowel disorders (which form part of a wider range of functional gastrointestinal disorders), has recently been reclassified by Thompson *et al.*^{1,2} The condition is defined as a functional bowel disorder in which abdominal pain is associated with defaecation or a change in bowel habit, with the additional features of disordered defaecation and abdominal distension. The insistence that both abdominal pain and disordered bowel habit must be present may be too restrictive, and many gastroenterologists make a positive clinical diagnosis of the condition even if abdominal pain is only a minor, infrequent symptom or is absent, provided that the other characteristic features are present. Currently accepted definitions of functional gastrointestinal disorder, functional bowel disorder, and the irritable bowel syndrome are outlined in box 1. Although different symptom complexes clearly exist that enable a symptom based classification to be made, no pathophysiological evidence exists that these are different conditions each with a fundamentally different cause and development; such a classification is vital, however, when patients are enrolled in research studies to maximise the possibilities for comparability between different centres.

Diagnostic criteria

In 1978 Manning *et al* described several abdominal symptoms that were more likely to be present in the irritable bowel syndrome than in organic abdominal disease (box 2).³ These symptoms were tested prospectively in subsequent studies and their validity confirmed. The more of these symptoms that are present, the more likely the patient is to have the irritable bowel syndrome.⁴ Kruis *et al* added other criteria, including a requirement for symptoms to have been present for more than two years and the use of symptom complexes that increase the chances of

Summary points

- The irritable bowel syndrome affects about 20% of adults in the industrialised world
- The condition is a disturbance of gastrointestinal function of unknown cause, but abnormalities of intestinal motility and visceral sensation are found in some patients
- Symptoms of the irritable bowel syndrome are often associated with extraintestinal manifestations, including urinary symptoms, dyspareunia, and fatigue
- Overall, 40-60% of patients with the irritable bowel syndrome who seek medical advice have psychological symptoms of depression or anxiety, or both
- Diagnosis of the irritable bowel syndrome can usually be made on the basis of clinical history and examination, but exclusion of organic disease is advisable in patients aged >45 years who present with new bowel symptoms
- No uniformly successful treatment exists for the irritable bowel syndrome. End organ treatment aimed at relieving abdominal pain (antispasmodic drugs) or disturbed bowel habit (antidiarrhoeal and bulking agents) can produce symptomatic relief, and "central" treatment (for example, anti-depressants, hypnotherapy, psychotherapy) should be considered in patients with associated affective disorders

making a positive clinical diagnosis.⁵ A recent report produced clear cut diagnostic criteria for the irritable bowel syndrome, which are particularly valuable as entry criteria for research studies (box 3).¹

Epidemiology

Several surveys show that functional gastrointestinal symptoms occur in up to a fifth of adults in the industrialised world.^{6,7} A recent community study found symptoms typical of irritable bowel syndrome in more than a fifth of women and a tenth of men and that prevalence was similar throughout life.⁷ Women seem to present more commonly than men to doctors with symptoms of the condition, although prevalence of symptoms in the community is similar in men and women. The irritable bowel syndrome is a transcultural disorder, with a similar prevalence reported in China, India, Japan, and South America, although prevalence

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Box 1—Functional disorders of the gastrointestinal tract²

Functional gastrointestinal disorder

A variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. Some symptoms may be attributable to the oropharynx, oesophagus, stomach, biliary tree, small or large intestine, or anus

Functional bowel disorder

A functional gastrointestinal disorder with symptoms attributable to the middle or lower intestinal tract. The symptoms include abdominal pain, distension, and disordered defaecation

Irritable bowel syndrome

A functional bowel disorder in which abdominal pain is associated with defaecation or changes in bowel habit, and with features of disordered defaecation and with distension

may be lower in other parts of South East Asia and in Africa.¹ In the developing world symptoms of the irritable bowel syndrome might be more common in cities than rural areas. Only a minority of individuals with symptoms present to doctors. A recent survey of 854 employees of a single business community in the City of London showed that 16.6% had symptoms of the condition, but only a quarter of these people had consulted a doctor (J E Gomborone *et al*, unpublished observations).

The irritable bowel syndrome accounts for between a fifth and a half of referrals to gastroenterologists and thus represents a substantial workload for hospital specialists. In the United States the condition accounts for an estimated 2.4–3.5 million visits to physicians each year, and 2.2 million prescriptions are issued. Further financial implications result from days lost at work.

Cause and development of the irritable bowel syndrome

The failure to identify a specific cause of the irritable bowel syndrome or indeed to have a widely agreed understanding of its pathophysiological or psychophysiological processes makes it difficult to develop universally acceptable strategies for treatment. Several lines of investigation, however, have increased our understanding of the condition (box 4), although many would argue that the studies have raised as many questions as they have answered.

A DISORDER OF MOTILITY OF THE GUT?

The disturbance of bowel habit in the irritable bowel syndrome has led investigators for several decades to study several aspects of intestinal motility and transit. Initial studies focused on colonic motility using multiple, fine bore assemblies, initially perfused with water but more recently with solid state, pressure transducers. Because of the difficulties of placing manometric catheters throughout the colon most studies have focused on the sigmoid colon and the rectum. Few clear cut differences have emerged between healthy control subjects and patients with the irritable bowel syndrome.⁸ Some studies suggest that basal colonic motility is normal whereas others show that it is increased, particularly in patients in whom constipation is the main symptom. Trotman and Misiewicz, however, showed that patients with the irritable bowel syndrome had lower colonic pressures than healthy control subjects and patients with diverticular disease.⁹

The reasons for the diversity in these findings probably relate to the selection of patients and methodological differences, including manometric techniques, bowel preparation, and sedation. When the colon is stimulated, however, by eating, balloon distension, or cholecystokinin, investigators agree that the colon of patients with the irritable bowel syndrome is hyperreactive. Some studies show that patients in whom constipation is the main symptom have greater responses than those in whom diarrhoea is the main symptom.

Thus although the findings of colonic motility in the irritable bowel syndrome differ widely, the colon of patients with the condition seems to be more sensitive to physiological and possibly pathophysiological stimuli. In all of these studies, however, a substantial overlap exists between the measurements in control subjects and those in the patients with the irritable bowel syndrome, indicating that no pathophysiological marker of the syndrome exists in the colon.

As studies of colonic motility failed to provide an immediate answer for the development of the irritable bowel syndrome investigators looked for motility disturbances in the small bowel. As with colonic motility, however, their findings differed.⁸ A poten-

Box 3—Diagnostic criteria for the irritable bowel syndrome¹

At least three months of continuous or recurrent symptoms of:

- Abdominal pain or discomfort which is:
 - Relieved with defaecation and/or
 - Associated with change in frequency of stool and/or
 - Associated with a change in consistency of stool
- Two or more of the following, on at least a quarter of occasions or days:
 - Altered bowel frequency (>3 bowel movements a day or <3 bowel movements a week)
 - Altered form of stool (lumpy/hard or loose/watery stool)
 - Altered passage of stool (straining, urgency, or feeling of incomplete evacuation)
 - Passage of mucus
 - Bloating or feeling of abdominal distension

tially important new abnormality was detected during fasting motility—namely, “clustered contractions.” These are short bursts of intense activity separated by long intervals of rest. Some studies incorporating prolonged manometry of the small intestine found that clustered contractions occurred more often in patients with the irritable bowel syndrome than in healthy volunteers, although the fact that they occurred in individuals free of symptoms indicates that the contractions are not pathognomonic of the irritable bowel syndrome. Other studies, however, using similar methodologies, did not find any difference between patients with the irritable bowel syndrome and healthy volunteers. Some clustered contractions seem to coincide with episodes of abdominal pain.¹⁰ Manometry of the small intestine after meals has been studied, but again results differ in that some investigators believe that motility after meals is reduced in duration¹⁰ whereas others have found it to be normal.⁸ Acute stress has been shown to increase motility in the small bowel in some studies but inhibit it in others.⁸ Thus, although some evidence suggests that patients with the irritable bowel syndrome have abnormalities of motility in the small bowel, the heterogeneous findings make it difficult to put together a single,

Box 2—Symptoms more likely to be found in the irritable bowel syndrome than organic abdominal disease³

- Pain eased after bowel movement
- Looser stools at onset of pain
- More frequent bowel movements at onset of pain
- Abdominal distension
- Mucus in rectum
- Feeling of incomplete emptying

Box 4—Possible factors in the development of the irritable bowel syndrome

- Disordered motility of the gut:
 - Small intestine
 - Colon
 - Oesophagus and stomach
- Altered gut sensation:
 - Increased awareness of normal gastrointestinal events
 - Reduced sensation threshold for "pathophysiological" events
- Involvement of the central nervous system:
 - Altered central processing of end organ motor and sensory activity
 - Effect of mood on gastrointestinal function

unifying hypothesis for the cause and development of the irritable bowel syndrome.

The potentially important clinical correlate of intestinal motility—namely, intestinal transit—has also been studied. In cases of the irritable bowel syndrome in which diarrhoea is the main symptom both oro-caecal transit time and whole gut transit time have been shown to be reduced, although again these findings are not universal.⁸ Diversity may well be accounted for by differences in the selection of patients and in measurement techniques. Although apparent abnormalities of motility in the small intestine and colon and transit time have been identified, many inconsistencies exist, and it is difficult to invoke a hypothesis that suggests that the irritable bowel syndrome is due to a primary motor disorder of the gut.

A DISORDER OF SENSATION OF THE GUT?

Debate continues on whether the irritable bowel syndrome is a condition in which abnormal motility is normally perceived or in which normal motility is abnormally perceived. Several studies have shown that increased sensitivity to balloon distension of the rectum exists in patients with the irritable bowel syndrome.^{11,12} This sensitivity is not part of a global, lower pain threshold as tolerance of cold and other painful stimuli produce either normal or reduced pain perception scores.¹³ Not all investigators, however, have been able to reproduce this increased rectal sensitivity.¹⁴ although others have been able to reproduce typical abdominal pain with balloon distension in the large or small intestine.¹⁵ Increased visceral sensation in patients with the irritable bowel syndrome may be a component of the disorder,¹⁶ although this is probably not the primary defect, partly because a substantial overlap exists between sensation thresholds of patients with the irritable bowel syndrome and those of healthy volunteers.

PART OF AN IRRITABLE BODY?

The evidence reviewed so far does not support the view that the irritable bowel syndrome involves a primary motility disorder or a primary disturbance of visceral sensation in the intestine. Additional information suggests that disruption of central control mechanisms that modulate the motility and sensation of the gut is more important than primary end organ dysfunction. Increasing evidence suggests that the symptoms of the irritable bowel syndrome are often accompanied by upper gastrointestinal symptoms such as nausea, vomiting, and early satiety; urinary symptoms such as nocturia, frequency, urgency, and the feeling of incomplete emptying of the bladder; and dyspareunia.^{17,18} Evidence also suggests that extra-

abdominal associations exist, including hyperreactivity of the bronchi.¹⁹ Smooth muscle is a common factor in all of these extraintestinal locations, and it seems logical, therefore, to invoke a hypothesis that involves disruption of central control rather than a primary, multiorgan hyperreactivity or hypersensitivity. Thus instead of merely an irritable bowel, there might also be an irritable oesophagus, an irritable stomach, an irritable bladder, and irritable vagina, and possibly irritable bronchi—or simply an irritable body.

RESULT OF AN IRRITABLE BRAIN?

Little doubt exists that emotional factors can alter the function of the gut. Any acute stress, such as an examination or an interview, can produce bowel frequency, nausea, vomiting, or early satiety. These symptoms suggest that acute, stressful events can affect the entire gastrointestinal tract, possibly with the patterns of symptoms being determined by individual susceptibility. It is also well recognised that urinary frequency commonly accompanies anxiety or acute, stressful events. Specifically, acute anger has been shown to increase the motility index in the colon, and acute stresses such as loud music and being woken from sleep can promote abnormalities of motility in the small intestine in patients with the irritable bowel syndrome that are different from responses in controls.⁸ Similarly the increase in the motility index in the colon associated with anger can be exaggerated in patients with the irritable bowel syndrome. Several studies have shown that immediately before presenting with the irritable bowel syndrome patients had a significantly increased stress score compared with healthy individuals.²⁰

Hospital based studies have often shown an excess of psychological symptoms in patients with the irritable bowel syndrome compared with controls with organic gastrointestinal disease and healthy volunteers. Psychological symptoms include depression, anxiety, phobia, and somatisation. The patients seen in a hospital after referral either by a general practitioner or by another specialist may not be typical of those who remain in primary health care or do not consult a doctor at all. Whitehead *et al* studied subjects with the irritable bowel syndrome in the community and found that they had a similar psychological profile to healthy individuals without the condition.²¹ A community study in which my colleagues and I compared the psychological profiles of consulters, non-consulters, and controls free of symptoms from the same population showed that the consulters with the irritable bowel syndrome had significantly higher anxiety and depression scores than either the non-consulters or the controls.²² Sixty per cent of the consulters fulfilled the diagnosis criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised, including major depression (50%), anxiety disorder (43%), and dysthymia (7%). However, the consulters judged their own pain to be more severe, frequent, prolonged, and disruptive to daily living than the non-consulters did. But when the investigator blindly assessed the severity of symptoms in consulters and non-consulters he found no significant difference. These observations suggested that an individual's perception of his or her symptoms was important in determining whether he or she consulted a doctor. This finding was pursued further with questionnaires on attitude to illness, and consulters with the irritable bowel syndrome were clearly significantly more concerned about illness, particularly with respect to the subscales of disease phobia, hypochondriacal beliefs, and bodily preoccupation.²³ Interestingly, the non-consulters were also significantly different from the controls, with an intermediate position between these subjects and the consulters.

The findings that a substantial proportion of consulters with the irritable bowel syndrome have a mood disorder and that non-consulters have different attitudes to illness from subjects who are symptom free indicate that central mechanisms may play a part in symptom production. Many patients who present with the irritable bowel syndrome do not have classic symptoms of an affective disorder, and mild depression can often be missed. In fact the alteration of affect may be different from standard psychiatric criteria, as my colleagues and I have shown in studies of recognition memory.²⁴ A group of subjects with the irritable bowel syndrome, a group with depression, and a group of controls with organic disease were shown a series of positive, negative, and neutral words, and their memory was tested 30 minutes later to determine whether recognition memory was biased. As expected, the depressed patients recalled more negative words than the controls, but the patients with the irritable bowel syndrome were intermediate, which correlated well with their scores on the Beck depression inventory. However, the patients with the irritable bowel syndrome recalled substantially more negative words that were not included in the initial list than even the depressed patients. This finding seems to support the view that no clear parallel relation exists between depression scores and other measures of affect in patients with the irritable bowel syndrome.

A psychosomatic model for the irritable bowel syndrome

Evidence exists therefore of end organ dysfunction and possible abnormalities of central control of perception processing in consulters, and to a lesser extent in non-consulters, with the irritable bowel syndrome. No reproducible end organ pathophysiological or biochemical marker of the irritable bowel syndrome exists and the associated smooth muscle dysfunction or hypersensitivity in other parts of the body strongly suggests that central factors may have a primary role. Affective disorder may well determine whether a non-consulter becomes a consulter, but abnormal attitudes to illness may be present in non-consulters with the irritable bowel syndrome which makes them more likely to seek medical advice even in the absence of affective disorder.

Not all patients with the irritable bowel syndrome have a clinical or subclinical affective disorder. Indeed many have normal bowel function until an episode of travellers' diarrhoea or food poisoning disrupts bowel function. Little if any controlled evidence exists that such events truly precipitate the symptoms of the irritable bowel syndrome, but anecdotal accounts and frequent reference to this link in standard textbooks suggests that it may be correct. The model therefore must include a somatic component that could be evoked by, for example, infection, dietary indiscretion, food intolerance but then for some reason continues as chronic dysfunction despite resolution of the primary result.

The question that remains unanswered is: What comes first, the chicken or the egg? Is it (a) the affective disorder or attitudes to illness that leads to the production of abdominal symptoms or to heightened awareness of mild and clinically unimportant abdominal symptoms that were previously disregarded or (b) the chronic abdominal symptoms that produce the affective disorder or disturbed perception, or both, by increasing concern about serious illness that propagates the syndrome?

Further investigation will no doubt continue to explore this conundrum. Treatment strategies cannot await the final characterisation of the process of the

cause and development of the irritable bowel syndrome but must proceed on the information available, largely along symptomatic guidelines and the individual patient's requirements.

An approach to management

Gastroenterologists, general practitioners, and patients with the irritable bowel syndrome are under no illusions that no universally effective treatment exists for the condition. A review of controlled clinical trials of therapeutic agents in the irritable bowel syndrome reinforced this view and showed that most trials were flawed, and thus even those purporting to show therapeutic benefit should be questioned.²⁵ Clinicians who manage the condition tend to fall into two camps: (a) those who favour the end organ theory and (b) those who favour the central approach, searching for and treating masked affective disorder and using psychological or behavioural approaches, or both, to stress management and symptom control (box 5). The two approaches are not mutually exclusive and can be used in sequence or combination, and indeed many clinicians and patients keep a foot in both camps.

Box 5—Approaches to the management of the irritable bowel syndrome

- Consultation:
 - Be positive in diagnosis of the irritable bowel syndrome
 - Avoid overinvestigation in young patients (under 40-45 years)
- End organ treatment:
 - Explore dietary triggers
 - Give fibre for constipation
 - Give antidiarrhoeal drugs for bowel frequency
 - Give smooth muscle relaxants for pain
- Central treatment:
 - Physiological explanation of symptom production
 - Counselling
 - Psychotherapy, hypnotherapy, cognitive therapy
 - Antidepressants

CONSULTATION

The first consultation for a patient with the irritable bowel syndrome is critical. The time taken to explain possible mechanisms of symptom production, to reassure about fears of serious organic disease, and to explore potential social and psychological factors may have more long term benefit than any of the current drugs. The value of making a positive clinical diagnosis of the condition without resorting to exhaustive investigation to exclude an organic disorder has been stated many times.

DIET

Dietary modification is popular with patients, but other than the use of fibre in constipated patients, no firm recommendations can be given for specific dietary treatment. Some patients, however, are particularly sensitive to caffeine and foodstuffs that contain sorbitol, and withdrawal of these can often help. Similarly, other foods that seem to aggravate symptoms can be avoided, but highly complex exclusion diets have little to commend them in the treatment of the irritable bowel syndrome and may be counterproductive.

END ORGAN TREATMENT

Some patients with bowel frequency seem to benefit from an antidiarrhoeal preparation such as loperamide,

and abdominal cramps in others are relieved by a smooth muscle relaxant.²⁶ These agents are best used on a sporadic basis, as analgesics are used for a headache. The placebo response rate, however, is high in patients with the irritable bowel syndrome,²⁵ and so several preparations may work in the short term.

CENTRAL TREATMENT

Real therapeutic triumphs in the irritable bowel syndrome can arise from treating mild or masked affective disorders. The clinician may be reluctant to enter this often difficult and time consuming arena and may feel poorly prepared to take an appropriate treatment to its conclusion, be it pharmacological, psychological, or a combination of the two. Clinical trials support the use of psychotherapy and hypnosis in the irritable bowel syndrome²⁷⁻²⁹ whereas trials of antidepressants are less impressive.²⁵ However, antidepressants classically do not work in non-depressed patients, and thus correct selection of patients remains paramount. I and my colleagues have shown recently that antidepressants can alter intestinal motility and transit, and thus it may be helpful to take into account patterns of symptoms when choosing an antidepressant.

The tricyclic antidepressant imipramine slows intestinal transit and has inhibitory effects on manometry of the small bowel³⁰ whereas the serotonin reuptake inhibitor paroxetine accelerates motility in the small intestine.³¹ Thus, although both drugs may have similar efficacy in treating depression, a patient in whom the main symptom is constipation may benefit most from a serotonin reuptake inhibitor, whereas a patient with bowel frequency may benefit from an antidepressant with anticholinergic properties. It should not be inferred from this central approach that affective disorder is the cause of the irritable bowel syndrome, but it is clearly an important reason why patients with symptoms of the irritable bowel syndrome seek medical advice and one that is often supremely amenable to treatment.

Conclusion

Our knowledge of the complex neural and neuro-humoral communication systems between brain, mind, and gut is rudimentary and has proved difficult to study in humans. Nevertheless, it is within this network that the answers to the questions about the cause and development of the irritable bowel syndrome and related conditions lie. Methods for studying intestinal motor function, visceral sensation, and the central control of these in humans are relatively primitive, so we are unable to examine satisfactorily, for example, the direct relation between manometry, smooth muscle electrical activity, propulsive activity, and transit, all of which may be relevant in functional disorders of the gut. Even more challenging are the pathophysiological consequences in the gut of mood change and environmental stress.

Since the irritable bowel syndrome is so common it might be tempting to regard its consortium of symptoms as merely a variant of normality. For the individual with the condition this is unhelpful. We should use the limited knowledge that we have to provide realistic explanations for symptom production, accepting, for example, that we have no satisfactory explanation for the common occurrence of visible abdominal bloating.

Therapeutically, we need to consider: "Why is this person presenting with symptoms of the irritable bowel syndrome now? Is there evidence of an affective disorder?" This may be a more successful approach for relieving or reducing abdominal symptoms than end organ treatment. We must await new insights into the

central and local control of intestinal motor and sensory function before the next important step forward is possible.

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