

# Depression, Anxiety, and the Gastrointestinal System

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Functional disorders of the digestive system, such as irritable bowel syndrome, are often associated with affective disorders, such as depression, anxiety, panic, and posttraumatic stress disorder (PTSD). Some of these associations are observed not only in clinical populations, but also in population-based samples, suggesting a relationship with pathophysiologic mechanisms underlying both gastrointestinal (GI) dysfunction and certain affective disorders. Sustained and acute life-threatening stressors play an important role in the onset and modulation of GI symptoms as well as in the development of affective disorders and PTSD. A neurobiological model is proposed that attempts to explain the development of visceral hypersensitivity, the neuroendocrine and autonomic dysfunction characteristic of functional GI disorders, as well as the overlap with affective disorders.

*(J Clin Psychiatry 2001;62[suppl 8]:28–36)*

The close association of acute gastrointestinal (GI) symptoms with emotional factors is well established in the lay language in such expressions as “hating somebody’s guts” or having one’s stomach “tied in knots.” These common expressions point toward an implicit understanding of the intricate relationship between anger, fear, or anxiety and specific, generally aversive, visceral experiences related to the gut.<sup>1</sup> Consistent with this linguistic “evidence,” a close correlation between physiologic gut responses (mucosal blood flow, colonic contractions) and acute emotional states such as fear, anger, and sadness has been reported.<sup>2–7</sup> Similarly, a close correlation between chronically altered gut function and affective disorders is well known to the experienced clinician in both psychiatry and gastroenterology. However, the exact nature of this relationship remains to be determined.

From the psychiatrist’s viewpoint, the constellation of GI symptoms referred to as irritable bowel syndrome (IBS) and related, so-called “functional” GI disorders may be regarded as symptoms expected to be associated with certain affective states. Meanwhile, gastroenterology research has focused primarily on identifying pathophysiologic mechanisms specific to the gut, such as the altered physiology of smooth muscle or enteric nervous system

functioning. It is only recently that a convergence of research into brain/gut interactions and the effect of stress on such interactions has provided a scientific framework to explain the close relationship of gut function and emotion and that of functional GI symptoms and affective disorders.

## PREVALENCE OF FUNCTIONAL GI DISORDERS

The hallmark symptoms of IBS are chronic abdominal pain and discomfort.<sup>8</sup> Different sets of diagnostic criteria have been proposed to define these hallmark symptoms as a syndrome distinct from other functional disorders without pain and chronic abdominal pain disorders. The most recent are the Rome II criteria,<sup>9</sup> shown in Table 1.

IBS is the most common functional GI disorder, with worldwide prevalence rates ranging from 9% to 23%.<sup>10</sup> Several population-based studies have demonstrated that IBS symptoms are more common in women than in men, with prevalence ratios ranging from 2:1 to 3:1.<sup>11,12</sup> This increased prevalence may represent either a reporting bias, that is, women are more willing to disclose IBS-related symptoms, or a biological difference.

Not all individuals with IBS seek medical care for their symptoms. On the basis of epidemiologic studies<sup>13–15</sup> in different countries, 20% to 75% of individuals meeting IBS criteria will seek medical care for their symptoms at some point in their lives. The wide range appears to be related, in part, to differences in national health care systems and access to medical care.

## PREVALENCE OF AFFECTIVE DISORDERS IN IBS

### Treatment-Seeking Samples

Published data on the proportion of IBS clinic patients with psychiatric diagnoses, summarized by Creed,<sup>16</sup> are

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*The International Consensus Group on Depression and Anxiety held the meeting “Focus on Depression and Anxiety Disorders in General Medicine,” October 7–8, 1999, in Funchal, Madeira. The Consensus Meeting was supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.*

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**Table 1. Rome II Criteria<sup>a</sup>**

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features:  
 Relieved with defecation  
 Onset associated with a change in frequency of stool  
 Onset associated with a change in form (appearance) of stool

<sup>a</sup>Adapted from Thompson et al.<sup>9</sup>

**Table 2. Anxiety and Depression in Different Samples of Irritable Bowel Syndrome Patients Attending Gastroenterology Clinics (%)<sup>a</sup>**

Study	Phobias	Anxiety	Panic	Depression	Total
Blanchard et al <sup>17,b</sup>	14.0	37	0	6	56
Walker et al (ECA data) <sup>18</sup>	17.8	...	5.2	13.4	...
Walker et al (clinic) <sup>19</sup>	29	11	7	21	...
Toner et al <sup>20</sup>	...	32	...	32	59
MacDonald and Bouchier <sup>21</sup>	...	28	0	22	53
Guthrie et al <sup>22,b</sup> (therapy trial)	16	7	...	27.5	50.5
Lydiard et al <sup>23</sup>	26	26	43	23	...
Guthrie et al <sup>24</sup> (chronic attenders)	...	9.5	...	38.5	48
Blewett et al <sup>25</sup>	...	5	9.5	17.5	33
Blanchard et al <sup>26,b</sup>	...	41	...	13	53
Corney et al <sup>27,c</sup>	...	...	...	...	66

<sup>a</sup>Reprinted, with permission, from Creed.<sup>16</sup>

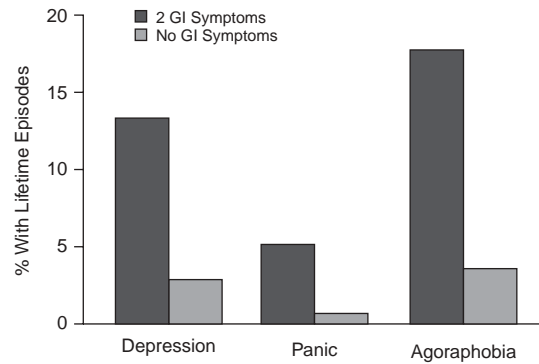
Abbreviation: ECA = Epidemiologic Catchment Area.

<sup>b</sup>Treatment studies.

<sup>c</sup>No details of diagnosis given.

shown in Table 2. Those studies with adequate patient numbers and a standardized psychiatric interview indicate that 50% to 60% of IBS patients in gastroenterology clinics have psychiatric disorders. The proportion is similar in patients entering treatment trials for IBS symptoms.<sup>16</sup>

The high prevalence of affective disorders in clinical samples of IBS patients could reflect (1) a high comorbidity in all affected patients, (2) a "self-selection hypothesis,"<sup>28</sup> or (3) a combination of the two. High comorbidity would be expected if the neurobiological or psychosocial mechanisms underlying affective disorders are related to central alterations in the generation of IBS symptoms. A self-selection hypothesis assumes that a patient with severe IBS symptoms is more likely to have psychiatric problems and states that only patients with the most severe and refractory IBS symptoms are selected into tertiary referral clinics, including psychiatric referrals. According to this hypothesis, the great majority of subjects with IBS symptoms, who either do not seek medical care or are seen in primary or secondary care, do not have a high prevalence of affective disorders. The third possibility would indicate that, while IBS and affective disorders share common central mechanisms, affective disorders alone influence health care-seeking behavior, regardless of the comorbid medical disorder.<sup>29,30</sup> For example, 40%<sup>23</sup> to 80%<sup>19</sup> of IBS patients reported that their psychiatric conditions were present before the onset of GI symptoms.

**Figure 1. Affective Disorders and Gastrointestinal (GI) Symptoms in a Population-Based Sample<sup>a</sup>**

<sup>a</sup>Data from Walker et al.<sup>18</sup>

### Population-Based Samples

Lydiard et al.<sup>31</sup> assessed the prevalence of GI symptoms (including an IBS "composite" of such symptoms) in individuals with panic disorder and other psychiatric disorders in a national community survey of 13,537 respondents (National Institute of Mental Health [NIMH] Epidemiologic Catchment Area [ECA] study). Individuals with panic disorder had the highest rate of unexplained GI symptoms (7.2%) compared with other diagnostic categories. For example, they had an almost 5-fold increased risk of an IBS-like composite of symptoms. Walker et al.<sup>18</sup> reviewed structured psychiatric interviews from nearly 19,000 subjects in the NIMH ECA study for the prevalence of GI distress symptoms and selected psychiatric disorders. The prevalence of unexplained GI symptoms in this sample of the general population ranged between 6% and 25%. As shown in Figure 1, subjects who reported 2 GI symptoms had significantly higher lifetime prevalence rates for depression, panic disorder, and agoraphobia than those who reported no GI symptoms.

In summary, although the ECA surveys were not designed specifically to determine the affective comorbidity rates of subjects with IBS symptoms, they suggest a strong association between affective and anxiety disorders and functional GI symptoms in subjects not seeking health care for their abdominal symptoms. Such an association would be consistent with hypotheses (1) and (3) discussed above.

### ANXIETY VERSUS DEPRESSION IN DIFFERENT IBS SAMPLES

Creed<sup>16</sup> has suggested that the relative prevalence of anxiety and depression varies significantly in different patient populations. Whereas symptomatic volunteers for treatment studies typically have phobias and anxiety disorders,<sup>17</sup> a greater proportion of refractory GI clinic attenders have depressive disorders<sup>22</sup> (see Table 2). For example,

**Table 3. Irritable Bowel Syndrome (IBS) Symptoms and Psychological Variables That Distinguish "Consulters" From "Nonconsulters" for IBS<sup>a</sup>**

Study	IBS Severity Symptoms	Psychological Variables
Heaton et al <sup>36</sup>	Bowel suffering score	Anxiety and depression
Drossman et al <sup>34</sup>	Pain severity	Depression score (MMPI)
	Diarrhea frequency	Illness behavior score (IBQ)
Kettell et al <sup>37</sup>	Pain severity	Health concerns
	Abdominal distension	Anxiety and depression
Talley et al <sup>11</sup>	Pain severity/frequency	...
	Daily activities interrupted	
van der Horst et al <sup>38</sup>	Pain severity	Somatic attribution
	Daily activities interrupted	Health concerns
	Additional symptoms	
Talley et al <sup>15</sup>	Pain severity and duration	...

<sup>a</sup>Reprinted, with permission, from Creed.<sup>16</sup>

Abbreviations: IBQ = Illness Behavior Questionnaire, MMPI = Minnesota Multiphasic Personality Inventory.

IBS patients recently referred to a gastroenterology practice have more anxiety than depression,<sup>32,33</sup> whereas chronic attenders with persistent or refractory GI symptoms have less anxiety (10%) than depression (39%).<sup>24</sup> One possible conclusion is that symptoms of anxiety (and the underlying pathophysiologic and psychosocial mechanisms) are closely related to IBS but the high rate of comorbid depression in chronic attenders is more closely related to the independent, enhancing effect of depression on health care-seeking behavior.<sup>29,30</sup> There are, however, other explanations. For example, increased anxiety in recently referred IBS patients may reflect higher anxiety about unexplained abdominal pain. Alternatively, depression is more likely to develop with chronicity; thus, the longer the duration of the stressor (and IBS symptoms), the greater the likelihood of depression. Also, there may be an older age at onset for depression than for most anxiety disorders, resulting in more depression in IBS patients who have had their symptoms for longer periods.

### ROLE OF AFFECTIVE DISORDERS IN DETERMINING HEALTH CARE-SEEKING BEHAVIOR

On the basis of 2 U.S. studies<sup>34,35</sup> in volunteers, psychological factors, including affective disorders and life stresses, are the primary predictors of health care-seeking behavior among individuals with IBS symptoms. It is assumed that psychological disturbances are not part of the medical syndrome, but influence which IBS patients seek health care. In contrast, a recent population-based study<sup>15</sup> in Australia found that over 70% of the sample had previously seen a doctor for their IBS symptoms. More importantly, neuroticism, psychological comorbidity, and a history of abuse did not explain health care-seeking behavior, whereas the severity and duration of abdominal

pain had statistically significant and independent effects on the probability of ever having sought care for abdominal pain and discomfort. Surprisingly, in the same study, only advancing age and visible abdominal distension had statistically significant and independent effects on the probability of seeking medical care *for any reason* within the past 12 months. Creed<sup>16</sup> recently summarized several studies comparing subjects who sought medical care for their IBS symptoms with those who did not. As shown in Table 3, the severity of abdominal pain was the most consistent factor distinguishing these 2 groups, whereas anxiety and depression were found less consistently. In the 2 population-based studies, psychological factors did not predict health care-seeking behavior for IBS symptoms.

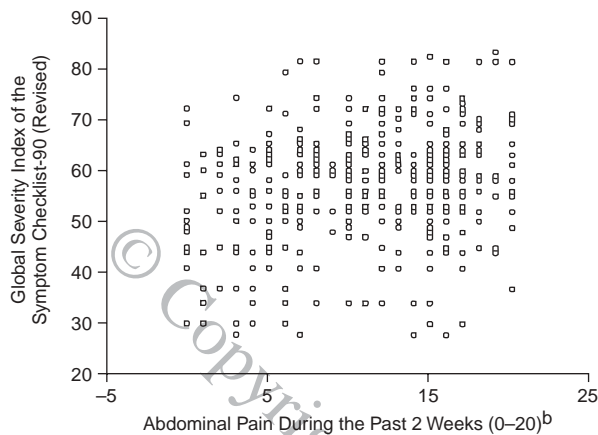
In summary, depression and anxiety are more prevalent in clinic populations of IBS sufferers compared with nonconsulting subjects having similar symptoms. These findings are consistent with similar reports on users of medical services in general.<sup>29,30</sup> However, when IBS studies were controlled for severity and duration of abdominal pain, the differences seemed to disappear. This suggests that increased anxiety and depression may be a function of more severe and more chronic abdominal pain in some IBS patients.

### ASSOCIATION BETWEEN GI SYMPTOM SEVERITY AND AFFECTIVE DISORDERS

According to the model proposed by Drossman and Thompson,<sup>28</sup> the severity of GI symptoms (self-reported by patients) is positively correlated with the prevalence of psychiatric diagnoses, such as depression and anxiety. It is assumed that psychological disturbances are not part of IBS, but influence the severity of IBS symptoms and health care-seeking behavior (see preceding paragraph). Drossman and Thompson<sup>28</sup> reported that only 1% of the most severe and refractory patients are referred to specialized referral centers and, in turn, to the psychiatrist (and/or surgeon); most IBS patients with mild and manageable symptoms are seen by the primary care physician. Similarly, Creed<sup>16</sup> has concluded that the poor response of IBS patients with comorbid affective disorders to medical treatment in several studies is related to the close association between psychological symptom severity and IBS symptom severity. However, it should be kept in mind that the great majority of current medical treatments for IBS are little better than placebo. Thus, rather than demonstrating a correlation between IBS symptom severity, refractoriness to treatment, and psychiatric comorbidity, IBS patients with anxiety and, particularly, depression may differ in their placebo response.

Correlations between anxiety, depression, and different GI symptoms have been reported in small clinical samples of IBS patients,<sup>16</sup> with correlation coefficients ranging between 0.21 and 0.63. In contrast, Lembo et al.<sup>39</sup> found no

Figure 2. Correlation of Irritable Bowel Syndrome Symptoms With Severity of Psychological Symptoms<sup>a</sup>



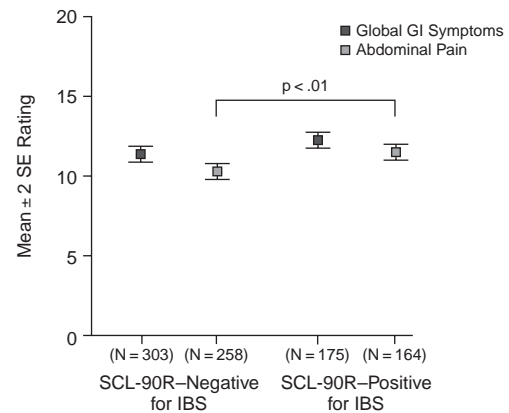
<sup>a</sup>B.D.N., E.A.M., unpublished data, July 1999.

<sup>b</sup>Measured by a 20-point rating scale with no pain at one end and maximum pain imaginable at the other.

difference in Symptom Checklist-90 (SCL-90) scores between patients who listed pain as their most bothersome symptom and those who listed other, nonpainful symptoms. We analyzed psychological distress and GI symptom severity in a large sample ( $N = 478$ ) of ROME I<sup>+</sup> positive IBS patients in a university-based functional GI program (B.D.N., E.A.M., unpublished data, July 1999). Thirty-five percent of patients had evidence of significant psychological distress, as defined by abnormal scores on 2 or more Symptom Checklist-90 (Revised) (SCL-90R)<sup>40</sup> scales or an abnormal score on the global severity index of the SCL-90R. As shown in Figure 2, we found no significant correlation between psychological distress and self-reported abdominal pain scores. Similarly, when we compared global GI symptom ratings or abdominal pain ratings between patients with elevated SCL-90R scores and those without, there were only small differences between the groups (Figure 3). These findings from a large clinical sample are consistent with previously reported findings in smaller clinical samples of IBS trial participants.<sup>24,36,41,42</sup> They show small correlations between psychological distress, presence of affective disorders, and severity of GI symptoms.

In summary, the following conclusions may be drawn: (1) Anxiety and depression correlate with reporting more severe IBS symptoms. (2) More severe IBS symptoms, specifically severity and frequency of abdominal pain, predict health care-seeking behavior, even after controlling for levels of anxiety and depression. (3) There appears to be a cyclical and self-perpetuating interaction between IBS symptoms and affective disorders: on the one hand, anxiety and depression elevate self-reported IBS symptom severity, and on the other hand, chronic IBS symptomatology may elevate anxiety and, particularly, depression.

Figure 3. Global Gastrointestinal (GI) Symptom Ratings and Abdominal Pain Ratings in Patients With and Without Elevated SCL-90R Scores<sup>a</sup>



<sup>a</sup>B.D.N., E.A.M., unpublished data, July 1999. Abbreviations: IBS = irritable bowel syndrome, SCL-90R = Symptom Checklist-90 (Revised). Mean abdominal pain ratings and global GI symptom ratings (rated on 20-point numerical severity scales) are only slightly different between IBS patients who were judged as positive for presence of psychological symptoms on the SCL-90R (1.00) and those who were not (0.00).

### ROLE OF LIFE STRESSES AND TRAUMATIC LIFE EVENTS IN IBS

IBS patients often report that stressful life events precede the onset or exacerbation of their symptoms. However, many scales of stressful life events measure the perceived impact of the stressor rather than its objective severity or the number of stressful life events. Perceived impact—how bad or how negative the event was—is closely tied to how anxious or depressed the person feels, so that in many ways, the measurement of life stressors becomes another index of anxiety and depression. In a questionnaire study<sup>43</sup> of 135 IBS patients and 654 controls, 73% of the patients and 54% of the controls reported that stress led to abdominal pain.

Stress also correlates with the number of bowel symptoms, disability days, and physician visits.<sup>44</sup> A prospective study<sup>45</sup> in IBS patients found that more than 90% of the variance in IBS symptoms over a 16-month period was accounted for by prolonged, threatening stressors. In this study, stress was measured as the presence of significant and threatening life events (such as divorce or loss of a job) rather than the subjective response to typical events. Another recent study<sup>46</sup> demonstrated that more patients who developed IBS symptoms following an acute enteric infection reported having experienced a life event involving some disruption of personal relationships (Table 4). In addition, the postinfectious IBS group also experienced an excess of life events in the 3 months following the acute gastroenteritis. The greater susceptibility of IBS patients to certain types of environmental stressors may be related,

**Table 4. Multivariate Analysis of Demographic, Stool, and Psychological Variables as Predictors for Development of Postinfectious Irritable Bowel Syndrome<sup>a</sup>**

Variable	Relative Risk	Corrected Relative Risk (95% CI)	Significance
Life events	1.95	1.97 (1.72 to 2.35)	.001
Hypochondriasis	2.27	2.04 (1.75 to 2.49)	.008
Somatization	2.38	...	...
Neuroticism	2.49	...	...
Anxiety	2.72	...	...

<sup>a</sup>Reprinted, with permission, from Gwee et al.<sup>46</sup>  
Abbreviation: CI = confidence interval.

in part, to differences in somatic threat appraisal, poor coping skills, and inadequate belief systems regarding management of life stresses and symptoms.<sup>35</sup>

A history of major traumatic events (physical and/or sexual abuse) or major losses (the loss of a parent) during childhood are present more frequently in IBS patients than in healthy controls.<sup>47-49</sup> In a study<sup>50</sup> of women at the University of North Carolina, 53% of women with IBS had a history of abuse, whereas 37% of women with structural GI diagnoses gave such a history. A history of such traumatic life events is not specific to IBS, but is more common in any emotionally disordered group and in patients with other functional pain disorders.<sup>51</sup>

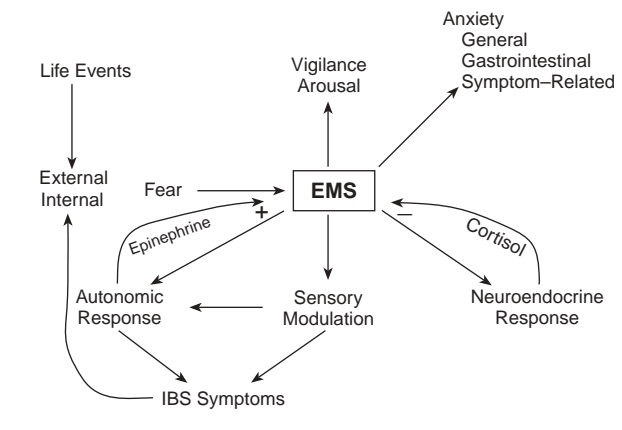
In summary, the data imply several pathways among IBS symptoms, negative affect, health care-seeking behavior, and life events. Recent studies on life events are consistent with a model in which sustained life events perceived as threatening by the affected individual have a major role in the development and modulation of IBS symptoms. To what degree the role of these life events in modulating IBS symptoms is independent of negative affect remains to be determined. Given the high prevalence of IBS symptoms in individuals who have undergone an acute life-threatening situation and have developed post-traumatic stress disorder (PTSD),<sup>52,53</sup> severe, acute threat may be included in this model as well.

In the following section, we will discuss possible central nervous system (CNS) mechanisms underlying the generation of IBS symptoms and associated affective disorders and the impact of stressful life events.

### EVOLVING DISEASE MODEL FOR FUNCTIONAL GI DISORDERS AND ASSOCIATED AFFECTIVE DISORDERS

Recent breakthroughs in the understanding of the central mechanisms involved in the generation of emotion and affective disorders make it possible to identify similarities between CNS mechanisms in affective disorders and the GI symptom complex referred to as IBS. In particular, the CNS networks activated in response to perceived threat or fear and those activated in response to learned (or condi-

**Figure 4. The Role of the Emotional Motor System (EMS) in Irritable Bowel Syndrome (IBS) and Affective Symptoms**



tioned) fear may play an important role in generating a conscious feeling of anxiety and GI symptoms.

### The Emotional Motor System

Figure 4 illustrates how the emotional motor system (EMS) has a central role in mediating the IBS symptoms of abdominal pain and discomfort and autonomic dysregulation of the gut, as well as associated central and peripheral responses. The term *emotional motor system* refers to a specific set of parallel motor pathways governing somatic, autonomic, antinociceptive, and endocrine responses of an organism<sup>54</sup> when its homeostasis is either threatened or perceived to be threatened. EMS activation may be associated with both acute and learned (conditioned) fear.

The close overlap of brain regions concerned with processing visceral afferent innervation, arousal, and central autonomic regulation of GI motility and secretory function may be important for the development of IBS symptoms involving both alterations in perception and autonomic responses to visceral events. The rostral portion of the anterior cingulate and medial prefrontal cortices represents the visceral motor cortex with projections to a network comprising hypothalamic nuclei, amygdala, and periaqueductal gray (PAG). The output of this network reaches nuclei within the brain stem (rostral ventral medulla, locus ceruleus, raphe nuclei) and is important in regulating pain modulation, arousal, and vigilance. In the context of enhanced fear responses, corticotropin-releasing factor (CRF)-containing projections, from the paraventricular nucleus of the hypothalamus and from the amygdala to both the locus ceruleus and the pituitary, are important in mediating the neuroendocrine, antinociceptive, and arousal responses to fear. Up-regulation of CRF message and enhanced CRF secretion in response to stressful stimuli have been implicated as a central component of the fear response in animal models of anxiety.<sup>55</sup>

In the context of learned fear, 2 components of the EMS play a crucial role in the organism's modulation of the pain experience: the amygdala and the PAG. The amygdala receives information about visceral stimuli, not only from the visceral motor cortex, but also from the thalamus, the nucleus parabrachialis, and the nucleus gigantocellularis. The latter input reaches the amygdala via noradrenergic projections from the locus ceruleus.<sup>56</sup> The central nucleus of the amygdala sends projections to the lateral and ventrolateral portions of the PAG, mediating opioid- and nonopioid-mediated analgesia.<sup>57-59</sup> The connections between the lateral and basolateral nucleus of the amygdala and the central nucleus contain glutaminergic synapses involving both *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors. The NMDA receptor is involved in long-term potentiation, an important mechanism in the development of emotional memory in the amygdala, in the context of fear conditioning.<sup>60</sup>

The locus ceruleus is an important link in the central pathways mediating fear responses and associated visceral responses: it is the primary source of ascending noradrenergic projections mediating arousal and forming a positive feedback loop with CRF-containing neurons in the amygdala.<sup>61,62</sup> Also, connections between the locus ceruleus and Barrington's nucleus, and from Barrington's nucleus to the primary parasympathetic nuclei, form the mechanism by which anxiety is linked to the characteristic responses of the GI tract: inhibition of gastric emptying and enhanced parasympathetic output to the left colon.<sup>63</sup> Evidence for an up-regulation of tyrosine hydroxylase and a down-regulation of noradrenergic autoreceptors on locus ceruleus neurons has been reported in animal models of anxiety<sup>55</sup> and functional visceral disorders.<sup>64</sup> The findings are consistent with hyperactivity of ascending noradrenergic arousal systems in affective and functional visceral pain syndromes.

### Alterations in Perception of Visceral Events

Enhanced perception of certain visceral stimuli, because of either greater sensitivity of visceral afferent pathways or central amplification of visceral afferent input, has emerged as an important theme in research into panic disorder and functional GI disorders, including IBS.<sup>65-67</sup> The clinical observations that led to the hypothesis of visceral hypersensitivity include recurring abdominal pain, tenderness on palpation of the sigmoid colon during physical examination, and excessive pain during endoscopic examinations of the sigmoid colon in IBS patients. Various studies have reported aspects of visceral psychophysiology: (1) IBS is associated with hypersensitivity in the upper GI tract as well as the colon,<sup>68,69</sup> (2) IBS is associated with heightened perception of normal intestinal contractions,<sup>70</sup> (3) IBS (unlike fibromyalgia) is not associated with a generalized hypersensitivity to noxious somatic stimulation,<sup>70,71</sup> and (4) the perception of colonic distensions is modifiable by attention, anxiety, and relaxation.<sup>72,73</sup>

Published experimental evidence from studies<sup>74-76</sup> assessing visceral sensitivity suggests that various perceptual abnormalities related to gastrointestinal stimuli may be more frequent in IBS patients. At least 2 perceptual alterations can be distinguished: (1) hypervigilance toward expected aversive events arising from the viscera, and (2) hyperalgesia inducible in certain IBS patients, but not in healthy controls, by sustained noxious visceral stimulation.

### HYPERVIGILANCE

Hypervigilance is an important component of the integrated response of the nervous system to perceived threat. Important pathways involved in mediating arousal and vigilance toward specific sensory stimuli are ascending monoaminergic arousal systems (including noradrenergic ascending systems) arising from nuclei in the brain stem and forebrain. Emotional reactions are typically associated with intense cortical arousal. Enhanced cortical arousal may be related to enhanced sensitivity toward visceral sensations associated with a particular emotional experience: urinary urgency, palpitations, and "butterflies" in the stomach are commonly reported by healthy individuals when experiencing fear. We will now review experimental studies that address hypervigilance toward visceral stimuli in patients with functional GI disorders.

Mertz et al.<sup>76</sup> found that IBS patients had a significantly lower median discomfort threshold for a 30-second rectal balloon stimulus compared with a normal population. In addition to lowered threshold, when 2 other perceptual abnormalities were considered (an abnormal area of sensory referral and/or increased intensity of rectal sensations during balloon distention), 95% of IBS patients had at least one abnormality. Only 7% of a control population displayed at least one of these 3 sensory findings. Other studies<sup>68,71,73,74,76-78</sup> have also found significant perceptual alterations in IBS populations including lowered discomfort thresholds for balloon distention of the small intestine, the colon, and the rectosigmoid. Similar findings of hypersensitivity have been reported for patients with functional dyspepsia<sup>66,79,80</sup> and noncardiac chest pain.<sup>81,82</sup> These findings are paralleled by target system hypersensitivity in other disorders such as fibromyalgia and myofascial pain disorder. The great majority of reported studies used study designs favoring the assessment of vigilance rather than hyperalgesia or allodynia. The role of cognitive factors, such as selective attention and vigilance, in modulating the perception of visceral input to the brain is also supported by preliminary results from brain imaging studies.<sup>83,84</sup>

### Altered Endogenous Pain Modulation of Noxious Visceral Stimuli

Patients with functional GI disorders, including those with IBS, show an enhanced perceptual response to repeated noxious distension of the viscera.<sup>85</sup> One way to ex-

plain these findings is by postulating an alteration in the balance of endogenous pain modulation systems, activated by the noxious repetitive stimulus, which, in turn, modulates spinal cord excitability.<sup>86,87</sup> Brain stem nuclei (rostral ventral medulla) send descending projections to the spinal cord dorsal horn that can facilitate or inhibit the excitability of neurons receiving afferent input from the viscera.<sup>88</sup> The balance between these inhibitory and facilitatory influences determines the amount of visceral afferent information that reaches supraspinal centers. Preliminary evidence from brain imaging studies suggests a compromised ability of IBS patients to activate brain regions, such as the PAG and the amygdala, that are prominently involved in activating the inhibitory component of these modulation systems.<sup>89</sup>

### **Role of Chronic Stress in Modulating Outputs of the Emotional Motor System**

There are neuroplastic and even structural changes in CNS circuits of the EMS in response to sustained severe life stresses.<sup>90-93</sup> In particular, chronic stress-induced presynaptic and postsynaptic changes in ascending monoaminergic arousal systems and in the neuroendocrine feedback systems (hypothalamic-pituitary-adrenal axis) have been reported in animal models and in human studies.<sup>94-97</sup> In selected patient populations, some of the target areas of these ascending systems, such as the hippocampus and medial prefrontal cortex, show structural changes after acute life-threatening stressors, such as severe abuse or severe PTSD.<sup>98</sup> On the basis of these findings, and the prominent role of the EMS in mediating IBS symptoms, we may speculate that similar neuroplastic mechanisms in response to threatening, sustained life events play a role in exacerbating symptoms in stress-induced IBS.

### **Altered Emotional Motor Responses to Acute and Conditioned Fear**

Analogous to concepts evolved to understand the pathophysiology of panic disorder, there is evidence for aversive interoceptive conditioning in most nonconstipated IBS patients.<sup>99</sup> Interoceptive conditioning refers to a learned fear response to previously innocuous physical sensations that have been paired with a painful or aversive stimulus. Classical conditioning of interoceptive stimuli has been well documented as a rapidly acquired, strong, and long-lasting phenomenon.<sup>100,101</sup> In panic disorder, interoceptive conditioning occurs when cardiovascular stimuli (racing heart, breathlessness) are associated with the terror of an unexpected panic attack. In IBS, interoceptive conditioning would occur when an innocuous gut sensation becomes a conditioned stimulus if it is paired with an unconditioned stimulus like GI distress. As a clinical example, the conditioned stimulus may be the sensation of even mild abdominal fullness, and the unconditioned stimulus the experience of abdominal pain. In another ex-

ample, the conditioned stimulus is mild physiologic stimulation of esophagus or stomach by even minimal oral intake, and the unconditioned stimulus is the development of abdominal pain or rectal urgency. In certain individuals, internal conditioning can make a previously innocuous stimulus a conditional cue that can reinstate abdominal distress. This type of conditioning is associated with hypervigilance toward the conditioned stimuli. Thus, vigilance and hypersensitivity to visceral sensations in IBS patients could reflect an underlying conditioning process.

Whereas patients with panic disorder show fear responses to cardiovascular visceral afferent information (their heart rate), nonconstipated IBS patients show evidence of physiologic fear responses to visceral information arising from the colon, such as fullness or urgency. In contrast to panic attacks, physiologic fear responses are often unassociated with the conscious feeling of anxiety. However, in a subset of IBS patients, strong feelings of anticipatory anxiety are associated with not being in the right place when the urge to have a bowel movement occurs. We may therefore assume that IBS patients associate fear with a neutral stimulus: normal sensations of fullness and urgency or the context in which such sensations might arise, such as food intake, time of day, and leaving the house. The fear response, triggered by a discrete stimulus or by contextual stimuli, manifests as exaggerated autonomic responses, an increased vigilance toward visceral afferent information arising from the GI tract (in particular the sensation of urgency), and inadequate activation of descending pain modulation systems.

## **CONCLUSIONS**

Considerable evidence suggests that certain affective disorders, in particular anxiety disorder and panic, occur with greater frequency in individuals with IBS symptoms, regardless of whether these individuals seek medical care for their abdominal symptoms. In addition, it appears that the higher prevalence of depression in chronic clinic attenders reflects, at least in part, the enhanced health care-seeking behavior of patients with depression. An evolving neurobiological model of IBS contains alterations in the central CRF and noradrenergic systems, which are also implicated in pathophysiologic models of anxiety. This evolving model implies that similar treatment strategies might be used to treat both GI symptoms and affective symptoms.

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