Irritable Bowel Syndrome and Sleep: Is there a Relationship?

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Irritable bowel syndrome (IBS) is a common chronic functional bowel disorder (Drossman et al., 1993; Thompson, Irvine, Pare, Ferrazzi, & Rance, 2002). The impact of IBS has been measured in the significant amount of health care resources used e.g., 8-10 doctor visits, 5 million prescriptions per year (Dean et al., 2005; Hahn, Saunders, & Maier, 1997; Hulisz, 2004; Sandler, 1990). The costs of IBS are high, and in 2000, the direct and indirect costs of diagnosis and symptom management of IBS were estimated to be 1.66 billion dollars, making it not only costly to the individual but also to the health care system (American College of Gastroenterology Functional Gastrointestinal Disorders Task Force, 2002; Brandt et al., 2002; Leong et al., 2003; Levy et al., 2001; Sandler et al., 2002). Leong and colleagues (2003) found that the total health care expenditures per year for the individual with IBS were 4527 dollars as compared to 3276 dollars for an age- and gender-matched control in 1998. Excess surgeries are among the health care events related to an IBS diagnosis (Feld et al., 2003). In a survey of over 4,000 IBS patients within an HMO system, 33% of women with IBS had a history of hysterectomy as compared 17% in the matched non-IBS group (Longstreth & Yao, 2004). In addition to health care utilization the impact of IBS has been measured in the poorer quality of life of patients as well as missed work and school(Whitehead, Burnett, Cook, & Taub, 1996). Several laboratories have used polysomnography (PSG) measures and have found inconsistent results with regard to objective sleep measures in IBS patients as compared to non-symptomatic individuals (Gorard, Vesselinova-Jenkins, Libby, & Farthing, 1995; Heitkemper et al., 2005; Orr, Crowell, Lin, Harnish, & Chen, 1997). These findings are in sharp contrast to the findings of self

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reported poor and unrefreshed sleep by patients with IBS. At the same time, recordings of autonomic nervous system (ANS) functioning during sleep have revealed important differences related to both symptom type and severity in women with IBS suggesting pathophysiologic links among sleep, ANS functioning, psychologicaldistress, and GI symptoms.

IBS is characterized by a constellation of GI symptoms outlined as the Rome criteria. These include: 1) abdominal pain relieved by a bowel movement or associated with changes in stool consistency and 2) fewer or more frequent stools, harder or looser stools, straining, urgency, feeling of incomplete evacuation or passage of mucus, and bloating or feeling of abdominal distention (American College of Gastroenterology Functional Gastrointestinal Disorders Task Force, 2002; Talley, Phillips, Melton, Wiltgen, & Zinsmeister, 1989). Individuals with IBS also self-report a number of non-GI symptoms. Among the most common are frequent awakenings, insomnia, and fatigue (Fass, Fullerton, Tung, & Mayer, 2000; Heitkemper & Jarrett, 1992; Maxton, Morris, & Whorwell, 1991; Walker, Roy-Byrne, & Katon, 1990).

IBS is a heterogeneous condition as exemplified by the differences in predominant symptoms (e.g., constipation, diarrhea, alternating stool pattern), symptom frequency (e.g., daily vs. weekly), and symptom severity (mild to very severe). Although clinicians have historically classified patients based on predominant bowel pattern there is evidence that symptom severity may be a critical determinant (Sach et al., 2002). Drossman et al. (2000) in a study of 211 women with moderate-severe functional bowel disorders (FBD) noted that women with severe symptoms had higher depression and psychological distress scores, poorer physical functioning and health-related quality of life (QOL), more maladaptive coping strategies, and greater health care utilization when compared to those with mild-moderate symptoms. Recently Creed reported that severity of abdominal pain was the principal predictor of impaired function and costs at baseline in IBS patients undergoing psychological treatment for IBS (Creed et al., 2005).

Limited evidence suggests that physiologic differences may also distinguish those with severe symptoms. Drossman et al. (2003) utilizing fMRI noted marked differences in an IBS patient over a 16 year period. During severe illness the patient had a low visceral pain threshold and activation of the midcingulate cortex, prefrontal area and somatosensory cortex with rectal distention. When the patient improved clinically there was no longer activation of these 3 brain areas along with increased tolerance of rectal distention. Our own work has shown that symptom severity as well as bowel symptom subgroup are associated with ANS balance indices (Burr, Heitkemper, Jarrett, & Cain, 2000; Heitkemper et al., 2001; Heitkemper, Jarrett, Lustyk, Cain, & Hertig, 1997). Taken together, self report and limited physiological data suggest than those reporting severe symptoms are more likely to utilize health care services, have greater psychological distress, report more somatic complaints, exhibit ANS imbalance, and different brain activation patterns.

IBS Etiology

It has been suggested that IBS may be a 3-component disorder characterized by dysfunctions in GI motor activity, visceral sensation and/or the processing of information by the CNS(see Figure

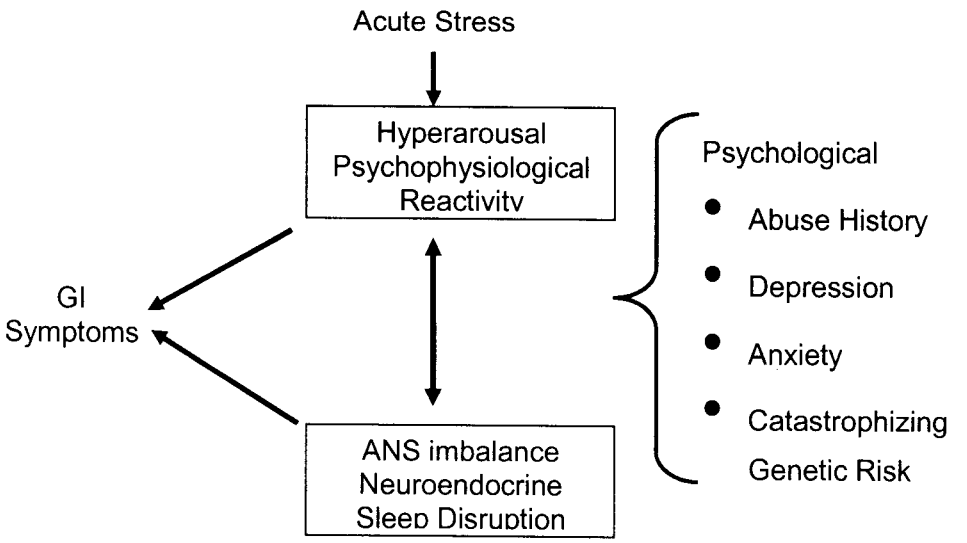

Figure Legend 1

Figure 1. Based on the literature to date we suggest the following model. Patients who self report severe IBS symptoms are hypervigilant to internal and external stimuli. This hypervigilance is manifested in psychophysiologic reactivity and is related to psychologic as well as genetic risk factors. Due to this hypervigilance, exposure to an acute stressor provokes a greater response in terms of ANS imbalance, neuroendocrine activation, sleep, and symptom experiences.

1) (Camilleri & Spiegel, 2002). GI motility is considered to play a role in symptom generation. Bowel pattern symptoms of IBS, e.g., constipation and diarrhea, suggest altered gut motility, however, methodological issues challenge the study of motility and symptom experiences in IBS. For example, swallowing manometry catheters may be difficult for patients with visceral hypersensitivity and recording in laboratory conditions may not mimic the environment in which symptoms are likely to occur (e.g., after meals, in response to stress). Using an ambulatory manometry to monitor left colon motility, Clemens, Samsom, Roelofs, van Berge Henegouwen, and Smout (2003) found only subtle differences in high amplitude propagated pressure waves that were related to the report of abdominal pain in 11 non-constipation prone IBS patients. Using electrogastrography (EGG) to look at the upper GI tract, van der Voort et al. (2003) noted a lack of postprandial increase in EGG amplitude in IBS patients relative to controls. In a report on 100 patients with alternating constipation and diarrhea, researchers found that IBS subjects on average had delayed gastric emptying and oral-cecal transit time as indicated by ultrasonography and hydrogen breath analyses, respectively (Portincasa, Moschetta, Baldassarre, Altomare, & Palasciano, 2003). Delvaux (2004) in a 2004 review summarized the motility findings to date in patients in IBS and concluded that IBS patients

exhibit an exaggerated colonic response to eating but few differences in intestinal motility. The lack of more dramatic findings may be related to the complexities of measuring motility in IBS patients, such as, the use of laboratory environments that may not mimic ambulatory conditions, variable measurement techniques, focus on upper vs. lower GI, small sample sizes in many studies, and limited generalizability of study findings to patients based on age and gender. In addition, there is often a lack of correlation between specific motility indices and actual symptoms reported by patients.

Numerous studies have provided data to implicate heightened visceral sensitivity in IBS (Accarino, Azpiroz, & Malagelada, 1995; Berman et al., 2002; Houghton, Calvert, Jackson, Cooper, & Whorwell, 2002; Hu & Talley, 1996; McKee & Quigley, 1993). Investigators have shown that stimulation of GI visceral afferents via balloon distention (i.e., barostat) results in differential responses in IBS versus non-IBS individuals (Accarino et al., 1995; Berman et al., 2002; Houghton et al., 2002; Hu & Talley, 1996; McKee & Quigley, 1993). In women with IBS, colonic visceral threshold was found to significantly lower threshold at menses relative to four other cycle phases (Houghton, Lea, Jackson, & Whorwell, 2002). Visceral hypersensitivity may also explain the role of specific dietary substances in IBS symptoms. Sorbitol, fructose, and lactose intolerance are associated with increased gas production and may subsequently trigger abdominal discomfort secondary to bowel lumen distention. Visceral hypersensitivity has also been linked to infectious conditions creating a new entity 'postinfectious IBS.' More recent data suggest that bacterial overgrowth may also contribute to visceral sensitivity in patients with IBS (Floch, 2005; Nuceraet et al., 2005). The fact that enhanced visceral sensitivity plays a role in IBS has led to several questions. For example, is IBS due to altered CNS processing of visceral input and, if so, at what level does this occur? Is IBS due to altered descending inhibitory influences that decrease visceral input? What role do stress and sleep play in IBS symptoms? Are IBS symptoms related to or due to over-stimulation of efferent output including the ANS and neuroendocrine systems subsequent to CNS activation?

IBS and Central Nervous System

The notion that CNS dysfunction may be present in IBS is supported by studies using both PET and functional MRI (fMRI). Silverman et al. (1997) showed that the perception of acute rectal stimulation was associated with anterior cingulate cortex activation in controls while IBS patients showed an aberrant brain activation pattern both during noxious rectal stimulation and in anticipation of rectal pain. Mayer, Naliboff, and Munakata (2000) have written on the role of the emotional motor system (EMS) in IBS. The EMS is a network of brain circuits that modulate arousal, visceral and somatic perception. Outputs of the EMS include ANS, neuroendocrine, attentional and pain modulatory responses (Ford, Camilleri, Hanson, Wiste, & Joyner, 1995). In particular, activation of the EMS via stressful stimuli can result in attentional arousal (hyperarousal) and subsequent sleep disturbances. This model posits that patients with IBS are sensitive or hypervigilant to environmental stress. Dickhaus et al. (2003) exposed IBS patients and controls to an acute stressor (noxious noise) and measured visceral sensitivity and ANS responses. Patients with IBS (n=15) showed heightened vis-

ceral sensitivity and increased heart rate during stress as compared to the relaxation phase. A stress versus relaxation difference in sensitivity was not observed in the non-IBS group (n=14) suggesting that IBS patients exhibit heightened visceral sensitivity in response to acute stress (Dickhaus et al., 2003). In another experiment IBS patients were found to be 'less distracted' by a mental stressor, i.e., showed no change in visceral sensitivity, as compared to controls (Posserud et al., 2004).

IBS and Autonomic Nervous System

The ANS provides the major linkage between the gut and the brain. Several investigators using laboratory ANS measures noted that symptom-specific IBS subgroups demonstrated different patterns of ANS abnormalities, i.e., diarrhea-prone subjects exhibited adrenergic and constipation-prone subjects exhibited parasympathetic nervous system (PSNS) dysfunction (Aggarwal et al., 1994; Elsenbruch & Orr, 2001). In addition, researchers demonstrated that when ANS activity was experimentally altered (i.e., increased sympathetic nervous system [SNS] activity) sensitivity to rectal stimulation was increased (Iovino, Azpiroz, Domingo, & Malagelada, 1995). Our laboratory has characterized ANS balance in IBS using several standardized laboratory measures (Valsalva maneuver, posture change) and acute stressor (Stroop Word Color Conflict test, ice water hand immersion) (Heitkemper et al., 2001; Levine, Jarrett, Cain, & Heitkemper, 1997). Physiologic measures have included heart rate (HR), skin temperature and blood pressure (BP), as well as 24 hour monitoring for HR variability (HRV). An overall finding is that as a group women with IBS have modestly increased resting HR and BP with few reactivity differences noted when compared as a group (i.e., no attention to predominant symptom) to control women (Heitkemper et al., 2001; Levine et al., 1997). However, this lack of overall differences in a heterogeneous patient group masks subgroup differences that exist when data are examined with respect to bowel function and symptom severity. For example, women who report severe constipation have reduced vagal tone and those who report severe pain not related to meals demonstrate increased vagal tone (Burret al., 2000). Others have also noted that ANS differences emerge when subgroup analyses are performed (Lee et al., 1997; Robert, Orr, & Elsenbruch, 2004; Thompson et al., 2002). Measuring 24 hour HRV in diarrhea-predominant patients, Lee et al. (1997) found increased PSNS tone and decreased SNS tone relative to controls. Combined these studies have provided evidence that ANS differences need to be viewed within the context of patient subpopulations characterized by specific symptoms and symptom severity. In a recent study Waring, Chui, Japp, Nicol, and Ford (2004) noted that a mixed symptom group of thirty women with IBS (ages 18-50) exhibited SNS dominance in response to acute standard laboratory ANS testing measures (orthostatic changes, handgrip, deep breathing) as compared to thirty healthy controls. However, in this study there was insufficient power to examine diarrhea versus constipation subgroup differences. Similarly, van der Veeck found increases baroreflex sensitivity in IBS patients as compared to controls (van der Veek et al., 2005). Gender differences in ANS reactivity to a visceral stimulus in IBS patients has been described by Tillisch and colleagues (2005) with men demonstrating greater SNS and decreased PSNS activation. However, this

group found no differences based upon symptom severity or type. However, only symptoms and severity over the previous 24 hours were measured.

Sleep and IBS

A number of studies have demonstrated an association between self-report sleep disturbances and IBS (Goldsmith & Levin, 1993; Rotem et al., 2003). A descriptive study of women without and with IBS symptoms found that those in the IBS group reported disturbed sleep patterns (e.g., frequent awakenings, overall poor quality of sleep) (American College of Gastroenterology Functional Gastrointestinal Disorders Task Force, 2002). In an early study Goldsmith and Levin (1993) had 23 IBS patients (men and women) record perceptions of their sleep quality for 1 month. Of these, 74% rated themselves as poor sleepers at the onset of the study. Based on diary data, poor sleep was related to increased IBS symptom severity both the next morning ($p< 0.001$) and throughout that day ($p< 0.05$). Goldsmith concluded that poor sleep may provoke or worsen IBS symptoms. Unfortunately indicators of co-morbid conditions (e.g., depression, anxiety) that have also been associated with poor sleep were not measured. The link between self-report of poor sleep and GI symptoms was strengthened by studies from our laboratory in which psychological distress was used as a co-variate in women with IBS (n=36). In almost 50% of the women, self-report of poor sleep quality the night before correlated ($p< 0.05$) with GI symptoms the next day even when controlling for psychological distress (Jarrett et al., 1998). Although it could also be hypothesized that increased IBS symptoms may worsen sleep quality, our analysis showed no significant relationship in this direction.

Several studies have examined PSG sleep variables in patients with IBS (Elsenbruch, Thompson, Hamish, Exton, & Orr, 2002; Kumar, Thompson, Wingate, Vesselinova-Jenkins, & Libby, 1992; Orr, 1993; Robert et al., 2004; Rotem et al., 2003). In an early study Kumar et al. (1992), described PSG and intestinal motility in IBS patients and controls. Although there were no group differences in nighttime motility, the IBS group (n=6) had more REM sleep (i.e., more prolonged REM episodes) than the controls (n=6, $p< .01$). However, there were several significant confounding variables that were not controlled, e.g., 3/6 patients showed signs of sleep apnea, menstrual cycle phase in females, and psychological state, e.g., depression, that may alter the pattern of REM sleep (Benca, Obermeyer, Thisted, & Gillin, 1992; Orr, 1993). Orr (1993) reported on 10 IBS patients and 10 age- and sex-matched controls using laboratory PSG monitoring for 1 night and electrogastrography to measure motility. They also found that IBS patients spent a greater ($p< 0.05$) percent of time in REM (22%) compared to controls (15%). In a larger study of 31 IBS and 23 control women, Elsenbruch et al. (2002) reported that while self report of disturbed sleep was greater in the IBS group there were no differences in PSG variables (e.g., sleep stages, fragmentation). In a follow up study by Orr's laboratory (2004) women with IBS (n=70) who reported severe depressive symptoms and increased GI symptom severity were more likely to have sleep complaints and alterations in sleep architecture (i.e., increased REM latency) as compared to controls (Robert et al., 2004). However, only one night of data collection was performed in each of these studies (often considered the adaptation to the sleep laboratory night). Using both PSG and actigraphy, Rotem et

al. (2003) studied 14 IBS patients and 11 historic controls (patients with a history of snoring) and noted that IBS patients had more fragmented sleep characterized by higher arousal and awakening index and a longer wake period after sleep onset.

The mismatch between self-report sleep and PSG indicators of sleep has been noted in other populations (Bencaet et al., 1992; Lundh & Broman, 2000). Lundh and Broman (2000) proposed that psychological vulnerability factors can predispose persons to respond with 'sleep-interfering processes' to stressful life events and/or engage in dysfunctional sleep-interrupting processes. While this model was developed to explain the lack of consistency between subjective and objective sleep in patients with insomnia, it has application to other groups (e.g., IBS) in whom insomnia is a frequent complaint.

Stress and IBS

While it is not clear whether stress initiates IBS, it is accepted that stress can trigger or exacerbate symptoms in patients with IBS (Mayer, 2000; Whitehead, Crowell, Robinson, Heller, & Schuster, 1992). Stressors can be characterized as acute or chronic. Acute stress is defined as any immediate threat to the homeostasis of the organism. Acute stress is further defined as exposure to a limited environmental stressor (e.g., noxious light, noise), physiological stressor (e.g., hypovolemia, hypoxia), or psychological or interpersonal stressor (e.g., public speaking). In an earlier study using daily diaries and the Life Events Survey (LES, positive and negative life experiences) we found that prospective self report of daily stress was directly correlated with GI symptom severity in approximately half of the women with IBS and fewer women without IBS. However, we found no differences in LES between IBS and controls (Levy, Cain, Jarrett, & Heitkemper, 1997). Others have argued that chronic or long term stress has a greater effect on symptoms than daily stressors (Bennett et al., 1998; Naliboff et al., 2004). An underlying assumption about patients with IBS is that they are individuals who are chronically stressed (e.g., report more frequent or severe stressors) (Bennett, Tennant, Piesse, Badcock, & Kellow, 1998; Naliboff et al., 2004). Naliboff reported on the strong relationship of vital exhaustion (as an indicator of chronic stress) with symptom severity and quality of life in patients with heartburn (Naliboff et al., 2004). Spiegel utilized this concept to explain the reduced quality of life noted in patients with IBS (Spiegel et al., 2004).

With regard to IBS several paradigms have been used to look at either the ANS reactivity to acute stress (Iovino et al., 1995; Levine et al., 1997) or visceral sensitivity under conditions of acute stress (Dickhaus et al., 2003; Posserud et al., 2004). In both models patients with IBS demonstrate higher resting heart rates as compared to controls. In a recent study Posserud et al. (2004) compared IBS and control subjects on visceral sensitivity during mental math testing and found that sensory threshold increased in controls during mental stress but not in patients with IBS. Corticotropin-releasing factor (CRH) and adrenocorticotropic hormone (ACTH) levels were higher in IBS patients in response to stress as compared to controls suggesting physiologic differences in acute stress reactivity. No effort was made in that study to look at symptom predominant or symptom severity subgroups.

Hyperarousal can be defined as increased readiness or responsiveness to stress. It has been

suggested that patients with IBS are hypervigilant to physical symptoms and may ruminate about their symptoms contributing to the state of physiologic hyperarousal (Accarino, Azpiroz, & Malagelada, 1995; Chang, Mayer, Johnson, FitzGerald, & Naliboff, 2000). We have described higher levels of catecholamines and cortisol in first morning urine samples from IBS women as compared to controls suggesting that this hypervigilance persists during sleep (Heitkemper et al., 1996). Stress is often cited as one of the most common causes of sleep disturbances (Morin, Rodrigue, & Ivers, 2003). Individuals with insomnia report higher levels of stressful life events in the year preceding the sleep disturbance onset. Rubman (1991) found that the number of daily stressors correlated with more time spent awake and poorer sleep quality as compared to days with fewer stressors. In a recent study, Morin et al. (2003) examined stress, arousal, and coping skills in patients with primary insomnia. While there were no differences between good and bad sleepers in terms of number of stressors, poor sleepers perceived their lives as more stressful, used more emotion-focused coping strategies and reported higher arousal levels as compared to good sleepers. Thus stress exposure results in presleep hyperarousal and subsequent sleep disturbances (Morin et al., 2003). There has been little systematic study of this phenomenon in patients with IBS despite the common reports ofpoor sleep in this population.

Psychological Distress and Sleep

It is well documented that patients with IBS report more symptoms compatible with psychopathologic disorders, abnormal personality traits, psychological distress and sexual abuse (Delvaux, Denis, & Allemand, 1997; Heitkemper, Jarrett, Taylor, et al., 2001; Koloski, Talley, & Boyce, 2001; Motzer, Hertig, Jarrett, & Heitkemper, 2003). Moreover, levels of daily psychological distress have been shown to be positively associated with GI symptoms in women with IBS (Locke, Weaver, Melton, & Talley, 2004). The comorbidity of mood disorders with IBS necessitates careful attention to psychological distress as an important mediating variable. In a sample of 770 patients with IBS Spiegel et al. (2004) examined factors that independently predicted mental health related quality of life. Those factors predictive of lower mental health included tiring easily and difficulty sleeping. From the non-IBS literature it is known depression is associated with disturbances of sleep continuity, a reduction of slow wave sleep, a disinhibition of REM sleep, decreased REM latency, a prolongation of the first REM period and increased REM density (Berger, van Calker, & Riemann, 2003; Rotenberg et al., 2002; Shaffery, Hoffmann, & Armitage, 2003). Of these REM latency has received considerable attention since shortened REM latency is associated with depression. (The latency of REM sleep is the time elapsed between sleep onset and the first occurrence of REM sleep.) At the same time acute stress applied prior to bedtime has been associated with reduced REM latency.

Sleep, Autonomic Nervous System and IBS

It has been established that ANS tone changes in relation to sleep stages (Siegel, 2003). In particular, non-REM (NREM) sleep is associated with reduced SNS tone as compared to REM sleep. The

question of day/night and its relationship to ANS function in IBS was addressed through the use of 24 hour Holter monitoring. In an early report, women with IBS (n=82) demonstrated reduced vagal tone during sleep relative to controls (n=35) (Heitkemper, Jarrett, Lustyk, et al., 1997). In that initial study no attempt was made to classify subjects based on symptom subgroup/severity or to examine sleep stages. Thompson et al. (2002) examined HRV during sleep of patients with IBS (n=16), IBS plus dyspepsia (IBS+D, n=17), and controls (n=21) and found that those with IBS alone had substantial vagal withdrawal during REM sleep as compared to controls and IBS+D. They concluded that ANS measures during sleep could be used to differentiate IBS patient subgroups. In part our results differ from these findings. We found that only women with severe IBS-constipation (n=7) exhibit vagal withdrawal during REM while those with severe IBS-diarrhea (n=5) exhibit enhanced vagal tone as compared to controls (n=26) and those with mild symptoms (n=13) (see preliminary studies). As such, these results suggest that ANS balance during sleep may serve as an important marker of symptom severity and subtype in women and may provide clues to the role of the gut-CNS connection in IBS.

Serotonin Reuptake Transporter (SERT) Protein

SERT is expressed in the CNS, platelets, and epithelial cells of the GI tract and is responsible for the uptake of 5-HT into presynaptic terminals. It is mapped to the chromosome 17q11.1-q12. And is a length polymorphism in the promoter region of the SERT gene, 5-HTTLPR, codes for two different alleles, a long (l) form, and a 44bp shorter (s) version. The s allele has been found to be associated with reduced SERT expression compared to the l allele. The normal distribution of these alleles varies by ethnicity (geographical region). Pata et al. (2002) using a Turkish population examined a possible association between SERT polymorphisms and the different clinical patterns of IBS and found that the *l/s* genotype was present in 16 of 18 (88%) patients with IBS-diarrhea as compared to 34 of 92 (37%) controls. However, Camilleri et al. (2002) found a frequency of 48% for the *l/s* genotype in an American sample. With regard to IBS several studies have previously described the 5-HTTLPR polymorphism in IBS patients without detailed investigation of the relationship between allele distribution and physical or psychological distress. Pata et al. (2002), in a study of 57 Turkish patients with IBS and 94 controls, found that the *s/s* genotype frequency was higher in the IBS-constipation group as compared to healthy controls. Yeo et al. (2004) found that l/s was more common in women with IBS-diarrhea (the only symptom group studied) than controls. In contrast, Kim in a study of 256 IBS patients from the Midwestfound no association between SERT polymorphism and IBS stool symptoms (Kim et al., 2004). None of the studies described above concomitantly examined psychological state with IBS symptoms at the time of SERT determination. Two other SERT polymorphisms have been described in the literature (Lesch et al., 1996). The first encompasses a variable-number-tandem-repeat (VNTR) element of 17 bp in the second SERT intron, with common alleles containing nine (ST*in*2.9), ten (ST*in*2.10) and 12 (ST*in*2.12) copies of the repeat. The shorter, nine-repeat allele ST*in*2.9 has been associated with major depression and anxiety (Evans et al., 1997;

Ogilvie et al., 1996). Pata et al. (2002) found no association between this polymorphism and IBS in the study of Turkish patients described above. Given ethnic differences, this does not preclude its association with GI symptoms, psychological distress, and sleep in a different population. The second polymorphism encodes for a rare I425V variant with resulting constitutive activation of SERT transport activity (Kilic, Murphy, & Rudnick, 2003). Carriers of this mutation show a dramatically increased risk for anxiety disorders and substance abuse/dependence (Ozaki et al., 2003).

In addition to GI symptoms, adults with IBS commonly have co-morbid symptoms of depressive and anxiety disorders. This has been reported in adults who are recruited from the community (Jarrett et al., 2003), primary care (Smith et al., 2004), and gastroenterology practices (Caspi et al., 2003; Toner et al., 1990). Polymorphisms in the SERT gene have been the subject of investigation in patients with a primary diagnosis of depression or anxiety (Caspi et al., 2003; Sen, Burmeister, & Ghosh, 2004; Smeraldi, Benedetti, & Zanardi, 2003; Yu, Tsai, Chen, Lin, & Hong, 2002). The connection between the 5-HTTLPR length polymorphism of SERT and response to psychological distress was recently highlighted in a study by Caspi et al. (2003) who found that presence of the *l/l* genotype protected individuals from the depression-inducing effects of accumulated life stress, whereas presence of the s allele increased their vulnerability. This is particularly intriguing in view of the fact that patients suffering from severe IBS often report a history of adverse life events and show an increased prevalence of PTSD. Other characteristics of the SERT protein are being studied. Bellini et al. (2003) in a study of 12 women with IBS-diarrhea and 12 controls found that SERT was expressed on platelet membranes at a low density. There was also a low degree of affinity at its ligand binding site suggesting that the efficiency of 5-HT uptake by platelet SERT is reduced. Accordingly, more 5-HT is left in the synaptic space and available for binding to postsynaptic receptors for extended periods of time. At the level of the GI tract, this could result in bowel motility, secretion, and sensitivity changes. A reduced uptake capacity is consistent with observations of abnormal increases in postprandial 5-HT plasma levels in IBS-diarrhea patients (Bearcroft, Perrett, & Farthing, 1998). Moreover, targeted deletion of the SERT gene in transgenic mice resulted in an initial increment of intestinal motility with diarrhea, followed by a later onset of constipation (Chen et al., 2001). Abnormal patternsof density or affinity for platelet SERT have been previously detected in patients with neurologic or psychiatric disorders (Alverez et al., 1999; Belous et al., 2001). A number of studies have supported a link between stress and mood disorders with reduced expression of SERT (Shaffery et al., 2003). Using a SERT knockout mouse model, Lira et al. (2003) found differences in behavioral models including forced swim, shock avoidance, novelty suppressed feeding and tail suspension suggesting that the SERT mutation produces alterations in depression-like and stress-response behaviors. SERT polymorphism has also been related to negative affect and amygdala activity. Furmark et al. (2004) studied amygdala activation during social anxiety provocation in relation to SERT genetic variation in 17 patients with social phobia. PET was used to estimate amygdala blood flow during private and public speaking (baseline & anxiety conditions). Individuals with *s/s* or *s/l* genotypes exhibited significantly increased levels of anxiety-related traits, state anxiety, and enhanced

right amygdala responding to anxiety provocation, compared with *l/l* homozygous subjects. In this population genetic variation was associated with symptom severity and amygdala excitability.

Summary

Health care providers working with IBS patients are challenged in that the underlying pathophysiology remains poorly defined and treatments are not universally effective (American College of Gastroenterology Functional Gastrointestinal Disorders Task Force, 2002). Nurses often work with patients to identify factors provoking or alleviating symptoms and based on these observations hone strategies to manage symptoms. Understanding stress induced alterations in sleep and ANS function may provide important clues as to additional self-management strategies to test.

References

1. Accarino, A. M., Azpiroz, F., & Malagelada, J. R. (1995). Selective dysfunction of mechanosensitive intestinal afferents in irritable bowel syndrome. *Gastroenterology, 108,* 636-643.
2. Aggarwal, A., Cutts, T. F., Abell, T. L., Cardoso, S., Familoni, B., Bremer, J., & Karas, J. (1994). Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. *Gastroenterology, 106,* 945-950.
3. Alvarez, J. C., Gluck, N., Arnulf, I., Quintin, P., Leboyer, M., Pecquery, R., Launay, J. M., Perez-Diaz, F., & Spreux-Varoquaux, O. (1999). Decreased platelet serotonin transporter sites and increased platelet inositol triphosphate levels in patients with unipolar d10epression: effects of clomipramine and fluoxetine. *Clincal Pharmacology & Therapeutics, 66,* 617-624.
4. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. (2002). Evidence-based position statement on the management of irritable bowel syndrome in North America. *The American Journal of Gastroenterology, 97,* S1-S5.
5. Bearcroft, C. P., Perrett, D., & Farthing, M. J. (1998). Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut, 42,* 42-46.
6. Bellini, M., Rappelli, L., Blandizzi, C., Costa, F., Stasi, C., Colucci, R., Giannaccini, G., Marazziti, D., Betti, L., Baroni, S., Mumolo, M. G., Marchi, S., & Del Tacca, M. (2003). Platelet serotonin transporter in patients with diarrhea-predominant irritable bowel syndrome both before and after treatment with alosetron. *The American Journal of Gastroenterology, 98,* 2705-2711.
7. Belous, A. R., Ramamoorthy, S., Blakely, R. D., Factor, M. I., Dupin, A. M., Katasonov, A. B., Lozier, R. H., Beniashvili, A. G., Morozova, M. A., & Brusov, O. S. (2001). The state of the serotonin transporter protein in the platelets of patients with somatoform [correction of somatiform] disorders. *Neuroscience and Behavioral Physiology, 31,* 185-189.
8. Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and psychiatric disorders. A meta-analysis. *Archives of General Psychiatry, 49,* 651-668; discussion 669-670.
9. Bennett, E. J., Tennant, C. C., Piesse, C., Badcock, C. A., & Kellow, J. E. (1998). Level of chronic life stress predicts clinical outcome in irritable bowel syndrome. *Gut, 43,* 256-261.

10. Berger, M., van Calker, D., & Riemann, D. (2003). Sleep and manipulations of the sleep-wake rhythm in depression. *Acta Psychiatrica Scandinavica,* Suppl, 83-91.
11. Berman, S. M., Naliboff, B. D., Chang, L., Fitzgerald, L., Antolin, T., Camplone, A., & Mayer, E. A. (2002). Enhanced preattentive central nervous system reactivity in irritable bowel syndrome. *The American Journal of Gastroenterology, 97,* 2791-2797.
12. Brandt, L. J., Bjorkman, D., Fennerty, M. B., Locke, G. R., Olden, K., Peterson, W., Quigley,E., Schoenfeld, P., Schuster, M., & Talley, N. (2002). Systematic review on the management of irritablebowel syndrome in North America. *The American Journal of Gastroenterology, 97,* S7-26.
13. Burr, R., Heitkemper, M., Jarrett, M., & Cain, K. (2000). Comparison of autonomic nervous system indices based on abdominal pain reports in women with irritable bowel syndrome. *Biological Research for Nursing, 2,* 97-106.
14. Camilleri, M., & Spiegel, R. (2002). Irritable bowel syndrome: diagnosis and treatment. W. B. Saunders.
15. Camilleri, M., Atanasova, E., Carlson, P. J., Ahmad, U., Kim, H. J., Viramontes, B. E., McKinzie, S., & Urrutia, R. (2002). Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology, 123,* 425-432.
16. Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386-389.
17. Chang, L., Mayer, E. A., Johnson, T., FitzGerald, L. Z., & Naliboff, B. (2000). Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia. *Pain, 84,* 297-307.
18. Chen, J. J., Li, Z., Pan, H., Murphy, D. L., Tamir, H., Koepsell, H., & Gershon, M. D. (2001). Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: Abnormal intestinal motility and the expression of cation transporters. *Journal of Neuroscience, 21,* 6348-6361.
19. Clemens, C. H., Samsom, M., Roelofs, J. M., van Berge Henegouwen, G. P., & Smout, A. J. (2003). Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome. *The American Journal of Gastroenterology, 98,* 1838-1843.
20. Creed, F., Ratcliffe, J., Fernandes, L., Palmer, S., Rigby, C., Tomenson, B., Guthrie, E., Read, N., & Thompson, D. G. (2005). Outcome in severe irritable bowel syndrome with and without accompanying depressive, panic and neurasthenic disorders. *British Journal of Psychiatry, 186,* 507-515.
21. Dean, B. B., Aguilar, D., Barghout, V., Kahler, K. H., Frech, F., Groves, D., & Ofman, J. J. (2005). Impairment in work productivity and health-related quality of life in patients with IBS. *The American Journal of Managed Care, 11,* S17-26.
22. Delvaux, M. (2004). Alterations of sensori-motor functions of the digestive tract in the pathophysiology of irritable bowel syndrome. *Best Practice & Research. Clinical Gastroenterology, 18,* 747-771.
23. Delvaux, M., Denis, P., & Allemand, H. (1997). Sexual abuse is more frequently reported by

IBS patients than by patients with organic digestive diseases or controls. Results of a multicentre inquiry. French Club of Digestive Motility. *European Journal of Gastroenterology and Hepatology, 9,* 345-352.

24. Dickhaus, B., Mayer, E. A., Firooz, N., Stains, J., Conde, F., Olivas, T. I., Fass, R., Chang, L., Mayer, M., & Naliboff, B. D. (2003). Irritable bowel syndrome patients show enhanced modulation of visceral perception by auditory stress. *The American Journal of Gastroenterology, 98,* 135-143.
25. Drossman, D., Leserman, J., Li, Z., Keefe, F., Hu, Y., & Toomey, T. (2000). Effects of coping on health outcome among women with gastrointestinal disorders. *Psychosomatic Medicine, 62,* 309-317.
26. Drossman, D., Ringel, Y., Vogt, B., Leserman, J., Lin, W., Smith, J., & Whitehead, W. (2003). Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. *Gastroenterology, 124,* 754-761.
27. Drossman, Li. Z., Andruzzi, E., Temple, R. D., Talley, N. J., Thompson, W. G., Whitehead, W. E., Janssens, J., Funch-Jensen, P., Corazziari, E., et al. (1993). U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Digestive Disease Science, 38,* 1569-1580.
28. Elsenbruch, S., & Orr, W. C. (2001). Diarrhea- and constipation-predominant IBS patients differ in postprandial autonomic and cortisol responses. *The American Journal of Gastroenterology, 96,* 460-466.
29. Elsenbruch, S., Thompson, J. J., Hamish, M. J., Exton, M. S., & Orr, W. C. (2002). Behavioral and physiological sleep characteristics in women with irritable bowel syndrome. *The American Journal of Gastroenterology, 97,* 2306-2314.
30. Evans, J., Battersby, S., Ogilvie, A. D., Smith, C. A., Harmar, A. J., Nutt, D. J., & Goodwin, G. M. (1997). Association of short alleles of a VNTR of the serotonin transporter gene with anxiety symptoms in patients presenting after deliberate self harm. *Neuropharmacology, 36,* 439-443.
31. Fass, R., Fullerton, S., Tung, S., & Mayer, E. A. (2000). Sleep disturbances in clinic patients with functional bowel disorders. *The American Journal of Gastroenterology, 95,* 1195-2000.
32. Feld, A., Von Korff, M., Levy, R., Palsson, O., et al. (2003). Excess surgery in irritable bowel syndrome (IBS). Gastroenterology, 24, 388.
33. Floch, M. H. (2005). Use of diet and probiotic therapy in the irritable bowel syndrome: analysis of the literature. *Journal of Clinical Gastroenterology, 39,* S243-246.
34. Ford, M. J., Camilleri, M. J., Hanson, R. B., Wiste, J. A., & Joyner, M. J. (1995). Hyperventilation, central autonomic control, and colonic tone in humans. *Gut, 37,* 499-504.
35. Furmark, T., Tillfors, M., Garpenstrand, H., Marteinsdottir, I., Langstrom,B., Oreland, L., & Fredrikson, M. (2004). Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. *Neuroscience Letters, 362,* 189-192.
36. Goldsmith, G., & Levin, J. S. (1993). Effect of sleep quality on symptoms of irritable bowel syndrome. *Digestive Disease Science, 38,* 1809-1814.
37. Gorard, D. A., Vesselinova-Jenkins, C. K., Libby, G. W., & Farthing, M. J. (1995). Migrating motor complex and sleep in health and irritable bowel syndrome. *Digestive*

Disease Science, 40, 2383-2389.

38. Hahn, B. A., Saunders, W. B., & Maier, W. C. (1997). Differences between individuals with self-reported irritable bowel syndrome (IBS) and IBS-like symptoms. *Digestive Disease Science, 42,* 2585-2590.
39. Heitkemper, M. BR., Jarrett, M., Lustyk, K., Cain, K., & Hertig, V. (1997). Description of autonomic state in women with irritable bowel syndrome. *Gastroenterology, 112,* A746.
40. Heitkemper, M. M., & Jarrett, M. (1992). Pattern of gastrointestinal and somatic symptoms across the menstrual cycle. *Gastroenterology, 102,* 505-513.
41. Heitkemper, M., Jarrett, M., Burr, R., Cain, K. C., Landis, C., Lentz, M., & Poppe, A. (2005). Subjective and objective sleep indices in women with irritable bowel syndrome. *Neurogastroenterology & Motility, 17,* 523-530.
42. Heitkemper, M., Jarrett, M., Cain, K. C., Burr, R., Levy, R. L., Feld, A., & Hertig, V. (2001). Autonomic nervous system function in women with irritable bowel syndrome. *Digestive Disease Science, 46,* 1276-1284.
43. Heitkemper, M., Jarrett, M., Cain, K., Shaver, J., Bond, E., Woods, N. F., & Walker, E. (1996). Increased urine catecholamines and cortisol in women with irritable bowel syndrome. *The American Journal of Gastroenterology, 91,* 906-913.
44. Heitkemper, M., Jarrett, M., Lustyk, K., et al. (1997). Description of autonomic state in women with irritable bowel syndrome. Gastroenterology, 112, A746.
45. Heitkemper, M., Jarrett, M., Taylor, P., et al. (2001). Effects of sexual and physical abuse on symptom experiences in women with IBS. *Nursing Research, 50,* 15-23.
46. Houghton, L. A., Calvert, E. L., Jackson, N. A., Cooper, P., & Whorwell, P. J. (2002). Visceral sensation and emotion: a study using hypnosis. *Gut, 51,* 701-704.
47. Houghton, L., Lea, R., Jackson, N., & Whorwell, P. (2002). The menstrual cycle affects rectal sensitivity in patients with irritable bowel syndrome but not healthy volunteers. *Gut, 50,* 471-474.
48. Hu, W. H., & Talley, N. J. (1996). Visceral perception in functional gastro-intestinal disorders: disease marker or epiphenomenon? *Digestive Disease Science, 14,* 276-288.
49. Hulisz, D. (2004). The burden of illness of irritable bowel syndrome: current challenges and hope for the future. *Journal Managed Care Pharmacy, 10,* 299-309.
50. Iovino, P., Azpiroz, F., Domingo, E., & Malagelada, J. R. (1995). The sympathetic nervous system modulates perception and reflex responses to gut distention in humans. *Gastroenterology, 108,* 680-686.
51. Jarrett, M. E., Burr, R. L., Cain, K. C., Hertig, V., Weisman, P., & Heitkemper, M. M. (2003). Anxiety and depression are related to autonomic nervous system function in women with irritable bowel syndrome. *Digestive Disease Science, 48,* 386-394.
52. Jarrett, M., Heitkemper, M., Cain, K. C., Tuftin, M., Walker, E. A., Bond, E. F., & Levy, R. L. (1998). The relationship between psychological distress and gastrointestinal symptoms in women with irritable bowel syndrome. *Nursing Research, 47,* 154-161.
53. Kilic, F., Murphy, D. L., & Rudnick, G. (2003). A human serotonin transporter mutation causes constitutive activation of transport activity. *Molecular Pharmacology, 64,* 440-446.
54. Kim, H. J., Camilleri, M., Carlson, P. J.,

Cremonini, F., Ferber, I., Stephens, D., McKinzie, S., Zinsmeister, A. R., & Urrutia, R. (2004). Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. *Gut, 53,* 829-837.

55. Koloski, N. A., Talley, N. J., & Boyce, P. M. (2001). Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *The American Journal of Gastroenterology, 96,* 1340-1349.
56. Kumar, D., Thompson, P. D., Wingate, D. L., Vesselinova-Jenkins, C. K., & Libby, G. (1992). Abnormal REM sleep in the irritable bowel syndrome. *Gastroenterology, 103,* 12-17.
57. Lee, K., Rhee, P., Kim, J., et al. (1997). Assessment of autonomic tone over a 24-hour period in patients with irritable bowel syndrome. *Gastroenterology, 112,* A773.
58. Leong, S. A., Barghout, V., Birnbaum, H. G., Thibeault, C. E., Ben-Hamadi, R., Frech, F., & Ofman, J. J. (2003). The economic consequences of irritable bowel syndrome: a US employer perspective. *Archives of Internal Medicine, 163,* 929-935.
59. Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Muller, C. R., Hamer, D. H., & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527-1531.
60. Levine, B. S., Jarrett, M., Cain, K. C., & Heitkemper, M. M. (1997). Psychophysiological response to a laboratory challenge in women with and without diagnosed irritable bowel syndrome. *Research in Nursing & Health, 20,* 431-441.
61. Levy, R. L., Cain, K. C., Jarrett, M., & Heitkemper, M. M. (1997). The relationship between daily life stress and gastrointestinal symptoms in women with irritable bowel syndrome. *Journal of Behavioral Medicine, 20,* 177-193.
62. Levy, R. L., Von Korff, M., Whitehead, W. E., Stang, P., Saunders, K., Jhingran, P., Barghout, V., & Feld, A. D. (2001). Costs of care for irritable bowel syndrome patients in a health maintenance organization. *The American Journal of Gastroenterology, 96,* 3122-3129.
63. Lira, A., Zhou, M., Castanon, N., Ansorge, M. S., Gordon, J. A., Francis, J. H., Bradley-Moore, M., Lira, J., Underwood, M. D., Arango, V., Kung, H. F., Hofer, M. A., Hen, R., & Gingrich, J. A. (2003). Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. *Biological Psychiatry, 54,* 960-971.
64. Locke, G. R., 3rd, Weaver, A. L., Melton, L. J., 3rd., & Talley, N. J. (2004). Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *The American Journal of Gastroenterology, 99,* 350-357.
65. Longstreth, G. F., & Yao, J. F. (2004). Irritable bowel syndrome and surgery: a multivariable analysis. *Gastroenterology, 126,* 1665-1673.
66. Lundh, L. G., & Broman, J. E. (2000). Insomnia as an interaction between sleep-interfering and sleep-interpreting processes. *Journal of Psychosomatic Research, 49,* 299-310.
67. Maxton, D. G., Morris, J., & Whorwell, P. J. (1991). More accurate diagnosis of irritable bowel syndrome by the use of 'non-colonic'

symptomatology. *Gut, 32,* 784-786.
68. Mayer, E. A. (2000). The neurobiology of stress and gastrointestinal disease. *Gut, 47,* 861-869.
69. Mayer, E. A., Naliboff, B., & Munakata, J. (2000). The evolving neurobiology of gut feelings. *Progress in Brain Research, 122,* 195-206.
70. McKee, D. P., & Quigley, E. M. (1993). Intestinal motility in irritable bowel syndrome: is IBS a motility disorder? Part 1. Definition of IBS and colonic motility. *Digestive Disease Science, 38,* 1761-1772.
71. Morin, C. M., Rodrigue, S., & Ivers, H. (2003). Role of stress, arousal, and coping skills in primary insomnia. *Psychosomatic Medicine, 65,* 259-267.
72. Motzer, S. A., Hertig, V., Jarrett, M., & Heitkemper, M. M. (2003). Sense of coherence and quality of life in women with and without irritable bowel syndrome. *Nursing Research, 52,* 329-337.
73. Naliboff, B. D., Mayer, M., Fass, R., Fitzgerald, L. Z., Chang, L., Bolus, R., & Mayer, E. A. (2004). The effect of life stress on symptoms of heartburn. *Psychosomatic Medicine, 66,* 426-434.
74. Nucera, G., Gabrielli,M., Lupascu, A., Lauritano, E. C., Santoliquido, A., Cremonini, F., Cammarota, G., Tondi, P., Pola, P., Gasbarrini, G., & Gasbarrini, A. (2005). Abnormal breath tests to lactose, fructose and sorbitol in irritable bowel syndrome may be explained by small intestinal bacterial overgrowth. *Alimentary Pharmacology and Therapeutics, 21,* 1391-1395.
75. Ogilvie, A. D., Battersby, S., Bubb, V. J., Fink, G., Harmar, A. J., Goodwim, G. M., & Smith,C. A. (1996). Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet, 347,* 731-733.
76. Orr, W. C. (1993). The irritable bowel syndrome: in your dreams? *The American Journal of Gastroenterology, 88,* 781-783.
77. Orr, W. C., Crowell, M. D., Lin, B., Harnish, M. J., & Chen, J. D. (1997). Sleep and gastric function in irritable bowel syndrome: derailing the brain-gut axis. *Gut, 41,* 390-393.
78. Ozaki, N., Goldman, D., Kaye, W. H., Plotnicov, K., Greenberg, B. D., Lappalainen, J., Rudnick, G., & Murphy, D. L. (2003). Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. *Molecular Psychiatry, 8,* 895, 933-936.
79. Pata, C., Erdal, M. E., Derici, E., Yazar, A., Kanik, A., & Ulu, O. (2000). Serotonin transporter gene polymorphism in irritable bowel syndrome. *The American Journal of Gastroenterology, 97,* 1780-1784.
80. Portincasa, P., Moschetta, A., Baldassarre, G., Altomare, D. F., & Palasciano, G. (2003). Panenteric dysmotility, impaired quality of life and alexithymia in a large group of patients meeting ROME II criteria for irritable bowel syndrome. *World Journal of Gastroenterology, 9,* 2293-2299.
81. Posserud, I., Agerforz, P., Ekman, R., Bjornsson, E. S., Abrahamsson, H., & Simren, M. (2004). Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress. *Gut, 53,* 1102-1108.
82. Robert, J. J., Orr, W. C., & Elsenbruch, S. (2004). Modulation of sleep quality and autonomic functioning by symptoms of depression in women with irritable bowel syndrome. *Digestive Disease Science, 49,* 1250-1258.
83. Rotem, A. Y., Sperber, A. D., Krugliak, P.,

Freidman, B., Tal, A., & Tarasiuk, A. (2003). Polysomnographic and actigraphic evidence of sleep fragmentation in patients with irritable bowel syndrome. *Sleep, 26,* 747-752.

84. Rotenberg, V. S., Shami, E., Barak, Y., Indursky, P., Kayumov, L., & Mark, M. (2002). REM sleep latency and wakefulness in the first sleep cycle as markers of major depression: a controlled study vs. schizophrenia and normal controls. *Progress in Neuro-Psychopharmacology and Biology Psychiartry, 26,* 1211-1215.
85. Rubman, S. (1991). The relationships between stress, mood, and insomnia. Dissertation Abstracts.
86. Sach, J., Bolus, R., Fitzgerald, L., Naliboff, B. D., Chang, L., & Mayer, E. A. (2002). Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? *The American Journal of Gastroenterology, 97,* 3131-3138.
87. Sandler, R. S. (1990). Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology, 99,* 409-415.
88. Sandler, R. S., Everhart, J. E., Donowitz, M., Adams, E., Cronin, K., Goodman, C., Gemmen, E., Shah, S., Avdic, A., & Rubin, R. (2002). The burden of selected digestive diseases in the United States. *Gastroenterology, 122,* 1500-1511.
89. Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 127,* 85-89.
90. Shaffery, J., Hoffmann, R., & Armitage, R. (2003). The neurobiology of depression: perspectives from animal and human sleep studies. *Neuroscientist, 9,* 82-98.
91. Siegel, J. M. (2003). Why we sleep. *Scientific American, 289,* 92-97.
92. Silverman, D. H., Munakata, J. A., Ennes, H., Mandelkern, M. A., Hoh, C. K., & Mayer, E. A. (1997). Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology, 112,* 64-72.
93. Smeraldi, E., Benedetti, F., & Zanardi, R. (2002). Serotonin transporter promoter genotype and illness recurrence in mood disorders. *European Neuropsychopharmacology, 12,* 73-75.
94. Smith, G. D., Steinke, D. T., Kinnear, M., Penny, K. I., Pathmanathan, N., & Penman, I. D. (2004). A comparison of irritable bowel syndrome patients managed in primary and secondary care: the Episode IBS study. *The British Journal of General Practice, 54,* 503-507.
95. Spiegel, B. M., Gralnek, I. M., Bolus, R., Chang, L., Dulai, G. S., Mayer, E. A., & Naliboff, B. (2004). Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Archives of Internal Medicine, 164,* 1773-1780.
96. Talley, N. J., Phillips, S. F., Melton, J., 3rd., Wiltgen, C., & Zinsmeister, A. R. (1989). A patient questionnaire to identify bowel disease. *Annals of Internal Medicine, 111,* 671-674.
97. Thompson, J. J., Elsenbruch, S., Harnish, M. J., & Orr, W. C. (2002). Autonomic functioning during REM sleep differentiates IBS symptom subgroups. *The American Journal of Gastroenterology, 97,* 3147-3153.
98. Thompson, W. G., Irvine, E. J., Pare, P., Ferrazzi, S., & Rance, L. (2002). Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire.

Digestive Disease Science, 47, 225-235.

99. Tillisch, K., Mayer, E. A., Labus, J. S., Stains, J., Chang, L., & Naliboff, B. D. (2005). Sex-specific alterations in autonomic function among patients with irritable bowel syndrome. *Gut, 54,* 1396-1401.
100. Toner, B. B., Garfinkel, P. E., Jeejeebhoy, K. N., Scher, H., Shulhan, D., & Di Gasbarro, I. (1990). Self-schema in irritable bowel syndrome and depression. *Psychosomatic Medicine, 52,* 149-155.
101. van der Veek, P. P., Swenne, C. A., Vooren, H., Schoneveld, A. L., Maestri, R., & Masclee, A. A. (2005). Viscerosensory-cardiovascular reflexes: altered baroreflex sensitivity in irritable bowel syndrome. *American Journal of Physiology: Regulatory, Integrative & Comparative Physiology, 289,* R970-976.
102. van der Voort, I. R., Osmanoglou, E., Seybold, M., Heymann-Monnikes, I., Tebbe, J., Wiedenmann, B., Klapp, B. F., & Monnikes, H. (2003). Electrogastrography as a diagnostic tool for delayed gastric emptying in functional dyspepsia and irritable bowel syndrome. *Neurogastroenterology & Motility, 15,* 467-473.
103. Walker, E. A., Roy-Byrne, P. P., & Katon, W. J. (1990). Irritable bowel syndrome and psychiatric illness. *American Journal of Psychiatry, 147,* 565-572.
104. Waring, W. S., Chui, M., Japp, A., Nicol, E. F., & Ford, M. J. (2004). Autonomic cardiovascular responses are impaired in women with irritable bowel syndrome. *Journal of Clinical Gastroenterology, 38,* 658-663.
105. Weinryb, R. M., Osterberg, E., Blomquist, L., Hultcrantz, R., Krakau, I., & Asberg, M. (2003). Psychological factors in irritable bowel syndrome: a population-based study of patients, non-patients and controls. *Scandinavian Journal of Gastroenterology, 38,* 503-510.
106. Whitehead, W. E., Burnett, C. K., Cook, E. W., 3rd., & Taub, E. (1996). Impact of irritable bowel syndrome on quality of life. Digestive *Disease Science, 41,* 2248-2253.
107. Whitehead, W. E., Crowell, M. D., Robinson, J. C., Heller, B. R., & Schuster, M. M. (1992). Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared with subjects without bowel dysfunction. *Gut, 33,* 825-830.
108. Yeo, A., Boyd, P., Lumsden, S., Saunders, T., Handley, A., Stubbins, M., Knaggs, A., Asquith, S., Taylor, I., Bahari, B., Crocker, N., Rallan, R., Varsani, S., Montgomery, D., Alpers, D. H., Dukes, G. E., Purvis, I., & Hicks, G. A. (2004). Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut, 53,* 1452-1458.
109. Yu, Y. W., Tsai, S. J., Chen, T. J., Lin, C. H., & Hong, C. J. (2002). Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Molecular Psychiatry, 7,* 1115-1119.