Journal of Pediatric Gastroenterology and Nutrition
47:679–715 © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Functional Abdominal Pain: Time to Get Together and Move Forward

*Samuel Nurko and †Carlo Di Lorenzo

**Director, Center for Motility and Functional Gastrointestinal Disorders, Children's Hospital Boston, Boston, MA, and †Division Chief, Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, OH*

Functional gastrointestinal disorders (FGID) include a combination of chronic or recurrent symptoms not explained by known biochemical or structural abnormalities. They represent a challenging group of conditions that are frequently misdiagnosed in children and are associated with significant morbidity and high health care costs. They account for more than 50% of the consultations in pediatric gastroenterology practice and 2% to 4% of all general pediatric office visits (1). Quality of life in patients with FGID is substantially poorer than in the general population or in those suffering from asthma or migraine (2). Children diagnosed with functional abdominal pain (FAP) or irritable bowel syndrome (IBS) have more abdominal and other somatic pain, functional impairment, and psychiatric symptoms than controls at 5-year follow-up (3), and one third to half of affected children experience persistence of abdominal pain into adulthood. Other studies have suggested an association between childhood functional abdominal pain and long-term comorbidity including depression, anxiety, lifetime psychiatric disorders, social phobia, and somatic complaints (4).

In the last 5 years, interest in the study and recognition of FGID in children has escalated. Careful epidemiological studies have been conducted, diagnostic criteria have been proposed and validated, significant progress has been made in understanding the pathophysiological mechanisms underlying several of these conditions, and more evidence-based treatment approaches have been developed. The importance of a multidisciplinary approach to childhood FGID is now widely recognized, and functional disorders have gone from being conditions with the stigma of "being in the child's head" or that were associated with "nothing being wrong with the child" to entities that, much like migraines or fibromyalgia, are recognized as legitimate disorders with accepted neuroenteric and central nervous system dysfunctions. Despite these promising developments, clearly more research is needed to further advance the science underlying the pathophysiology and treatment of these conditions. An impediment to progress in the field has been the absence of a forum in which experts from different specialties can meet to discuss different aspects of FGID in children and establish an agenda for future research. The need to further study FAP and IBS in children was emphasized by the 2nd World Congress of Pediatric Gastroenterology Working Group for Neurogastroenterology (5). The American Academy of Pediatrics and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Committee on Abdominal Pain recently recommended to further investigate the presentation and diagnosis of FGID in children (6). The recent publication of the updated Rome criteria with the inclusion for the first time of 2 pediatric committees (7,8) also created momentum for additional studies in this field.

Based on this background, the symposium "New Insights Into Childhood Functional Abdominal Pain and Irritable Bowel Syndrome: A Multidisciplinary Approach" was designed to bring together basic and clinical scientists whose major clinical and research interest relates to the pathophysiology, evaluation, and treatment of childhood FAP, IBS, and related pain syndromes. The symposium was held on October 24, 2007 in Salt Lake City, UT, 1 day before the NASPGHAN annual meeting. It was cosponserd by NASPGHAN and the National Institutes of Health, and received funding from industry, foundations, and nonprofit institutions. The symposium was an unmitigated success, gathering the participation of more than 350 pediatric and adult gastroenterologists, basic scientists, psychologists, and many other pediatric subspecialists. The body of the symposium consisted of presentations focusing on the pathogenesis, diagnostic criteria, natural history, and treatment options as they pertain to pain predominant FGID in children. An innovative aspect included presentations on the evaluation and treatment of children with other pain syndromes unrelated to the gastrointestinal (GI) tract. The symposium provided opportunities for young scientists to

Address correspondence and reprint requests to Samuel Nurko, MD, MPH, Children's Hospital Boston, Gastroenterology/Nutrition, 300 Longwood Ave, Hunnewell Ground, Boston, MA 02115 (e-mail: Samuel.nurko@childrens.harvard.edu).

The authors report no conflicts of interest.

participate and interact with established investigators in the field. Finally, the symposium intended to develop a research agenda for collaborative studies to define the pathophysiology and treatment strategies for childhood FAP.

During the symposium the biopsychosocial model was endorsed to provide a framework to integrate the biological and psychosocial components of FGID. The biopsychosocial model assumes that the individual genetic background and early life experiences influence the biological and psychosocial predisposition to symptom development in response to a variety of physiological or noxious stimuli later in life. This response is affected by physical, environmental, and social exposures that influence the patient's attitude toward illness.

The first module of the symposium discussed the basic and pathophysiological mechanisms underlying FGID, including the role of early life events, genetics, and environment. Given that the biopsychosocial model has been adopted by investigators dealing with non-GI functional disorders, such as fibromyalgia, autonomic dysfunction, and migraine, experts from non-GI disciplines were asked to share their experiences in the second module of the symposium. The absence of a consistent biological marker in FGID has led to the development of symptom-based criteria to diagnose these disorders. The third module was dedicated to discussion of the Rome criteria (7–9). Finally, the last didactic module discussed medical, behavioural, and complementary treatment strategies for pediatric FGIDs.

The end of the symposium was dedicated to the discussion of a research agenda and the creation of a pediatric multicenter consortium for the study of FGIDs, and brought together representatives from the National Institutes of Health, industry, and many interested pediatric gastroenterologists. The following summaries provide the current state of knowledge as it was presented at the symposium.

Acknowledgment: The symposium was sponsored in part by NIH grant 1R130K080536-01 and by NASPGHAN, Nationwide Children's Hospital, PEOS, Procter & Gamble, TAP Pharmaceutica, and the Rome Foundation.

REFERENCES

1. Starfield B, Hoekelman RA, McCormick M, et al. Who provides health care to children and adolescents in the United States? *Pediatrics* 1984;74:991–7.
2. Frank L, Kleinman L, Rentz A, et al. Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases. *Clin Ther* 2002;24:675–89.
3. Stordal K, Nygaard EA, Bentsen BS. Recurrent abdominal pain: a five-year follow-up study. *Acta Paediatr* 2005;94:234–6.
4. Hotopf M, Carr S, Mayou R, et al. Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study. *BMJ* 1998;316:1196–200.
5. Di Lorenzo C, Benninga MA, Forbes D, et al. Functional gastrointestinal disorders, gastroesophageal reflux and neurogastroenterology: working group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2004;39 (Suppl 2):S616–25.
6. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:245–8.
7. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut* 1999;45 (Suppl 2):II60–8.
8. Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
9. Caplan A, Walker L, Rasquin A. Validation of the pediatric Rome II criteria for functional gastrointestinal disorders using the questionnaire on pediatric gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 2005;41:305–16.

Genetics and Functional Bowel Disease

Nicholas J. Talley

Chair, Department of Internal Medicine, Mayo Clinic, Jacksonville, FL

There are thought to be several distinct functional gastrointestinal disorders, but all of them remain largely mysterious in terms of the underlying pathogenesis (1). Several lines of evidence now support the hypothesis that genetic factors and gene–environment interactions are important in the pathogenesis of these disorders.

Address correspondence and reprint requests to Nicholas J. Talley, MD, PhD, Mayo Clinic College of Medicine, Division of Gastroenterology, PL-6, 200 First St, Rochester, MN 55905 (e-mail: talley.nicholas@mayo.edu).

The author reports no conflicts of interest.

FAMILIAL CLUSTERING

Both irritable bowel syndrome (IBS) and functional dyspepsia (FD) may cluster in families. Locke et al found an increased risk for subjects with IBS and dyspepsia reporting a first-degree relative with abdominal pain

and/or bowel disturbance (2). This did not apply to spousal controls, even adjusting for potential confounders such as age, sex, and somatization, but a limitation was that the results were based on self-report. In IBS, these results were subsequently confirmed by screening the first-degree relatives of IBS cases and spousal controls (3). Familial clustering, however, could be explained by common early environmental factors and/or genetic factors.

GENES VERSUS ENVIRONMENT

One method to dissect genetic from environmental effects is twin studies. A large study from the United Kingdom using the Rome II criteria for IBS failed to identify any increased concordance of IBS in monozygotic (MZ, or genetically identical) twins versus dizygotic twins (sharing half the same genes) (4). Four other twin studies, from Australia (5), the United States (6,7), and Norway (8), have identified an increased concordance for IBS in MZ twins, although the strength of the association has varied. The definitions of IBS used in 3 of these positive studies (5,6,8) were less specific than the Rome II criteria. This may suggest that the specific IBS phenotype described by the Rome criteria does not have a genetic component, but a US twin study applying Rome II criteria supports a genetic contribution (7).

One key advance has been the recent identification of a possible gene–environment interaction. In the Norwegian twin study (8), the presence of restricted fetal growth (<1500 g) was a significant risk factor for the development of IBS, with the onset of IBS appearing a mean of 7.7 years earlier in low birth weight babies. Furthermore, MZ twins with IBS (vs no IBS) had significantly lower birth weights (8). This gene–environment interaction requires confirmation, but it may indicate that impaired maturation of the nervous system interacts with key genes in inducing IBS-like features (9).

COMORBID PSYCHIATRIC DISEASE AND IBS

Although it is well established that psychiatric diagnoses are more common in patients with IBS (1), whether this is explained by any common genetic or early environmental factors is unknown. One hypothesis is that the genes that predispose to IBS are the same genes that predispose to depression; however, recent work using co-twin analysis (focusing solely on MZ twins) suggests that this is unlikely (10,11).

CANDIDATE GENE TESTING

Single nucleotide polymorphisms are common genetic variations that occur by chance and, if functional, produce human diversity (12). A number of attempts have been made to find an association between functional single nucleotide polymorphisms and IBS or FD that theoretically may be relevant to the pathogenesis. As with many other shotgun-like approaches, the results have been inconclusive. Although some individual studies have suggested that a functional polymorphism for the gene-encoding activity of the serotonin transporter was associated with IBS (12,13), a meta-analysis concluded there was no such association present (14). More excitement has been generated by the finding of a G-protein polymorphism (GNbeta 3) in functional dyspepsia, with the homozygous CC genotype linked to functional dyspepsia in 2 independent studies (15–17). A positive association of IBS and an interleukin-10 polymorphism has also been reported (18), but work with other candidate genes in cytokine or receptor pathways to date has been convincingly negative (12,14).

This does not mean that there may not be important genes that account for some cases of IBS or FD. For example, patients with a mutation in a sodium channel gene (*SCN5A*) were significantly more likely to report gastrointestinal symptoms, especially abdominal pain, versus those that did not have this mutation, suggesting a possible link (19). The gene association studies have generally been too small, however, and many of the positive results probably reflect type I error, whereas the negative findings may reflect type II error. Furthermore, no genome-wide scans have yet been reported, although the challenges of adequately defining the phenotype remain a key concern.

CONCLUSIONS

The field of genetics of functional bowel disorders is in its infancy but remains potentially exciting. There is growing evidence that functional bowel disorders do run in families, and some of this clustering is likely to be genetic or due to gene–environment effects. Applying a broad definition, there is convincing evidence that the concordance of at least IBS is increased in identical twins. Psychiatric comorbidity in IBS does not appear to be explained by a common genetic link. Rigorous and large genetic epidemiology studies are now needed to identify the relevant functional genes. Such research is likely to lead to changes in our current concepts of the phenotype of IBS and FD. The work also has the potential to progress the concept of individualized medicine to our patients living with these common and often debilitating problems.

REFERENCES

1. Talley N, Spiller RC. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360:555–64.

2. Locke GR III, Zinsmeister AR, Talley NJ, et al. Familial association in adults with functional gastrointestinal disorders. *Mayo Clin Proc* 2000;75:907–12.
3. Kalantar JS, Locke GR III, Zinsmeister AR, et al. Familial aggregation of irritable bowel syndrome: a prospective study. *Gut* 2003;52:1703–7.
4. Mohammed I, Cherkas LF, Riley SA, et al. Genetic influences in irritable bowel syndrome: a twin study. *Am J Gastroenterol* 2005;100:1340–4.
5. Morris-Yates A, Talley NJ, Boyce PM, et al. Evidence of a genetic contribution to functional bowel disorder. *Am J Gastroenterol* 1998;93:1311–7.
6. Levy RL, Jones KR, Whitehead WE, et al. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 2001;121:799–804.
7. Lembo A, Zaman M, Jones M, et al. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. *Aliment Pharmacol Ther* 2007;25:1343–50.
8. Bengtson MB, Ronning T, Vatn MH, et al. Irritable bowel syndrome in twins: genes and environment. *Gut* 2006;55:1754–9.
9. Talley NJ. Genes and environment in irritable bowel syndrome: one step forward. *Gut* 2006;55:1694–6.
10. Wojczynski MK, North KE, Pedersen NL, et al. Irritable bowel syndrome: a co-twin control analysis. *Am J Gastroenterology* 2007;102:2220–9.
11. Whitehead WE. Twin studies used to prove that the comorbidity of major depressive disorder with IBS is NOT influenced by heredity. *Am J Gastroenterology* 2007;102:2230–1.
12. Saito YA, Petersen GM, Locke GRI, et al. The genetics of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; 3:1057–65.
13. Saito YA, Locke GRR, Zimmerman JM, et al. A genetic association study of 5-HTT LPR and GNbeta3 C825T polymorphisms with irritable bowel syndrome. *Neurogastroenterol Motil* 2007;19:465–70.
14. Geeraerts B, Van Oudenhove L, Tack J. Serotonin transporter gene polymorphisms in irritable bowel syndrome. *Neurogastroenterol Motil* 2006;18:957–9.
15. Holtmann G, Siffert W, Haag S, et al. G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. *Gastroenterology* 2004;126:971–9.
16. Camilleri CE, Carlson PJ, Camilleri M, et al. A study of candidate genotypes associated with dyspepsia in a U.S. community. *Am J Gastroenterol* 2006;101:581–92.
17. Holtmann G, Talley NJ. Hypothesis driven research and molecular mechanisms in functional dyspepsia: the beginning of a beautiful friendship in research and practice? *Am J Gastroenterol* 2006;101: 593–5.
18. Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003;52:91–3.
19. Locke GR 3rd, Ackerman MJ, Zinsmeister AR, et al. Gastrointestinal symptoms in families of patients with an SCN5A-encoded cardiac channelopathy: evidence of an intestinal channelopathy. *Am J Gastroenterol* 2006;101:1299–304.

Early Life Events and the Development of Visceral Hyperalgesia

Adrian Miranda

Assistant Professor of Pediatrics, Division of Pediatric Gastroenterology, Medical College of Wisconsin, Milwaukee

The pathophysiology of functional bowel disorders in children such as irritable bowel syndrome (IBS) and functional abdominal pain is poorly understood. Enhancement of visceral sensitivity to physiological and noxious stimuli seems to be the hallmark of functional pain. Nociceptive neuronal circuits, formed during the neonatal period, normally require use-dependent activity for appropriate development. Noxious stimuli or stress during this critical period may alter their development and subsequently result in decreased pain thresholds later in life. The question of whether adverse events experienced in early life can prime a child to develop chronic abdominal pain is one that has only recently received much attention. Animal and human data suggest that there are at least 4 putative mechanisms that may help explain the development of visceral hypersensitivity following early life pain or stress: sensitization of central (spinal) neurons, sensitization of primary sensory neurons, impaired stress response (hypothalamic-pituitary-adrenal axis), and/or altered descending inhibitory control.

Address correspondence and reprint requests to Adrian Miranda, MD, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226 (e-mail: amiranda@mcw.edu).

The author reports no conflicts of interest.

SPINAL NEURONAL SENSITIZATION

Sensitization of spinal sensory neurons can result in enhanced neurotransmission, increased neuronal spontaneous activity, and decreased firing thresholds. Recent evidence suggests that neonatal rat exposure to

either repetitive colorectal distension (CRD) or colonic irritation results in permanent alterations in spinal dorsal horn neurons and subsequent chronic visceral hyperalgesia in adulthood (1). Similar results are obtained if a noxious stimulus is given early in development in areas of viscero-somatic convergence. For example, we have previously shown that noxious somatic stimulation in the gastrocnemius muscle of neonatal rats results in sensitization of CRD-sensitive spinal neurons and chronic visceral hyperalgesia in adult rats (2). This is not surprising because most spinal neurons that receive input from the visceral afferents in the thoraco-lumbar and the lumbo-sacral spinal cord also receive convergent synaptic input from afferents of the deep somatic domain. Thus, somatic pain experienced during a time of great neuronal plasticity such as trauma or surgery may influence the response and behavior of spinal neurons, resulting in sensitization and a decreased threshold for pain. Infants with prior surgery have been shown to require higher fentanyl dosages intraoperatively, display greater postoperative distress, and require higher doses of morphine postoperatively (3). Similarly, infants with prenatally diagnosed hydronephrosis demonstrate increased abdominal sensitivity compared to controls, which is an example of convergent viscero-somatic inputs (4).

SENSITIZATION OF PRIMARY SENSORY NEURONS

Visceral sensation is a complex process that involves transmission of impulses that start in the gut and travel through the spinal cord via afferent nerves. The enteric nervous system, often termed the ''little brain,'' has as many neurons as the spinal cord. The lower sensory threshold in patients with functional pain or IBS may reflect increased signaling from the peripheral gut (ie, sensitization of intramural mechanoreceptors) that occurs following low-grade inflammation or immune activation early in development. Previous studies show that colonic irritation in neonatal rats sensitizes primary sensory neurons in the lumbosacral region and results in higher neuronal spontaneous firing and response to colorectal distension (5). This may occur though a variety of potential mechanisms including increased expression of receptor molecules involved in nociceptive pathways, alteration of ionic channel properties (ie, *N*-methyl-D-aspartate, 5-hydroxytryptamine, transient receptor potential vanilloid receptor 1, natural killer), or the presence of inflammatory mediators. The severity and frequency of abdominal pain in patients with IBS has been shown to correlate with the presence of activated mast cells in proximity of nerve endings in the gut wall (6). Furthermore, not all patients with IBS or functional abdominal pain have somatic complaints, which supports a peripheral mechanism involved in the enhanced pain transmission. It is important to realize that sensitization early in life may not result in the development of symptoms but may prime or predispose a child to the development of hyperalgesia later in life when re-exposed to injury or stress. The effect of a second attack has been shown in a neonatal rat model of bladder inflammation (7).

IMPAIRED HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Stress and anxiety are known triggers for symptoms of functional pain and IBS. Children with early life stress are more likely to develop IBS (8). Thus, it seems likely that adverse early life events can alter the stress response and bowel sensitivity later in life. The central corticotropin releasing factor (CRF) system has been implicated in mediating the effects of early life stress and may contribute to the development of abnormal reactivity of the hypothalamic-pituitary-adrenal axis. Rats pups exposed to 180 min of maternal separation for the first 2 weeks of life develop acute and delayed stress-induced visceral hyperalgesia to CRD (9). The stress of maternal separation has also been shown to increase CRF-like immunoreactivity and mRNA levels in the periventricular nucleus, locus coeruleus, and amygdala of adult rats (10). We have recently shown that stress associated with orogastric suctioning in neonatal rat pups induces visceral and somatic hyperalgesia in adult rats and that the visceral hyperalgesia is prevented with preemptive administration of the CRF1 receptor antagonist, antalarmin (11). Furthermore, administration of antalarmin inhibits colonic hypersensitivity in rats known to have high anxiety (12). In humans the effects of peripheral CRF include decreased threshold to rectal distension and increased motility (13). Peripheral administration of a CRF-receptor antagonist to patients with IBS improves gastrointestinal motility, visceral perception, and negative mood in response to gut stimulation (14).

ALTERED DESCENDING INHIBITORY CONTROL

Processing of incoming pain signals in the spinal cord is subject to descending modulatory control from the brain, which can be inhibitory or facilitatory. The descending inhibitory control, or ''pain gate,'' occurs through endogenous opioids and is postulated to play a role in a variety of chronic pain syndromes. The descending inhibitory controls are known to be immature at birth. Thus, persistent noxious sensory inputs in the immature spinal cord may not be properly modulated, ultimately altering inhibitory processing in the adult spinal cord. Recent animal data support this concept. Nalaxone, an opioid receptor antagonist, has no effect on rats following maternal separation but significantly increases visceral hypersensitivity in nonhandled rats, suggesting a diminished pain inhibitory opioidergic tone in animals with

early life stress (9). In addition, the efficacy of fentanyl in response to rectal distension is greater in patients with IBS as compared with normal controls (15). This points to a diminished release of endogenous opioids that may involve the descending inhibitory system.

Taken together, these data constitute a compelling case that adverse early life events such as pain or stress can induce long-term changes in the nociceptive circuitry. Significant work remains to be done to answer the precise mechanistic questions that underlie the behavioral outcome in humans.

REFERENCES

1. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 2000;119:1276–85.
2. Miranda A, Peles S, Shaker R, et al. Neonatal nociceptive somatic stimulation differentially modifies the activity of spinal neurons in rats and results in altered somatic and visceral sensation. *J Physiol* 2006;572:775–87.
3. Peters JW, Schouw R, Anand KJ, et al. Does neonatal surgery lead to increased pain sensitivity in later childhood? *Pain* 2005;114: 444–54.
4. Andrews KA, Desai D, Dhillon HK, et al. Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. *Pain* 2002;100: 35–46.
5. Lin C, Al-Chaer ED. Long-term sensitization of primary afferents in adult rats exposed to neonatal colon pain. *Brain Res* 2003;971:73–82.
6. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126:693–702.
7. Deberry J, Ness TJ, Robbins MT, et al. Inflammation-induced enhancement of the visceromotor reflex to urinary bladder distention: modulation by endogenous opioids and the effects of early-in-life experience with bladder inflammation. *J Pain* 2007;8:914–23.
8. Lowman BC, Drossman DA, Cramer EM, et al. Recollection of childhood events in adults with irritable bowel syndrome. *J Clin Gastroenterol* 1987;9:324–30.
9. Coutinho SV, Plotsky PM, Sablad M, et al. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol Gastrointest Liver Physiol* 2002;282:G307–16.
10. Plotsky PM, Thrivikraman KV, Nemeroff CB, et al. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. *Neuropsychopharmacology* 2005;30:2192–204.
11. Smith C, Nordstrom E, Sengupta JN, et al. Neonatal gastric suctioning results in chronic visceral and somatic hyperalgesia: role of corticotropin releasing factor. *Neurogastroenterol Motil* 2007;19:692–9.
12. Greenwood-Van Meerveld B, Johnson AC, Cochrane S, et al. Corticotropin-releasing factor 1 receptor-mediated mechanisms inhibit colonic hypersensitivity in rats. *Neurogastroenterol Motil* 2005;17:415–22.
13. Nozu T, Kudaira M. Corticotropin-releasing factor induces rectal hypersensitivity after repetitive painful rectal distention in healthy humans. *J Gastroenterol* 2006;41:740–4.
14. Sagami Y, Shimada Y, Tayama J, et al. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut* 2004;53:958–64.
15. Lembo T, Naliboff BD, Matin K, et al. Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. *Pain* 2000;87:137–47.

Ecology of Functional Gastrointestinal Disorders

Miguel Saps

Assistant Professor, Department of Pediatrics, Northwestern University Medical School, Chicago, IL

Ecology is the science that studies the interactions of organisms with their environment and each other. Two important principles of ecology characterize environmental relations. First, all living organisms have a continual interrelation with other living and nonliving elements that comprise their environment. Second, each of these ecosystems and their components are connected and affect one another.

Address correspondence and reprint requests to Miguel Saps, MD, 2300 Children's Plaza, Box 57, Chicago, IL 60614 (e-mail: MSaps@childrensmemorial.org).

The author reports no conflicts of interest.

Sixty years ago, the World Health Organization provided a new dimension to the concept of human health by including physical, psychological, and social components to its definition. In keeping with this holistic concept of health, the biopsychosocial model underscores the relation and equilibrium among biological, physiological, and psychological systems to determine susceptibility to functional gastrointestinal disorders and explain the clinical variability and different responses to treatment (1). This model proposes that illness and disease result from biological, psychological, and social subsystems that interact at multiple levels. In this context, psychosocial factors have direct physiological and pathological consequences.

This framework differs from the classical view of a single etiology for each condition. Equilibrium between organ systems and ecosystems results in health, whereas imbalance is experienced as illness.

Our interaction with the environment can be loosely characterized as an interdependent relation between 2 ecosystems. Food antigens and gut flora are examples of the complex internal ecosystem. Relevant examples of the external ecosystem are the surrounding social and physical environment.

Adverse reactions to food are frequently reported by patients with functional gastrointestinal disorders (FGIDs) (2). There are intriguing but still preliminary data indicating a possible role of food hypersensitivity in the pathogenesis of irritable bowel syndrome (IBS). A trial of food elimination based on serum immunoglobulin G4 antibodies in patients with IBS has shown a significant decrease in symptoms, compared with patients receiving a sham diet (3). In line with these findings, another study showed improvement in rectal compliance in patients with IBS undergoing a food-specific immunoglobulin G4 antibody-guided exclusion diet (4).

The gut flora influences our body functions in multiple ways. The flora forms a barrier against pathogens, stimulates the host immune system, limits the adhesion of pathogenic bacteria to the epithelium, and controls the proliferation and differentiation of epithelial cells (5). Germ-free rats have different spatial and temporal characteristics of migrating motor complexes in the small intestine than do conventional animals (6). Anaerobic bacteria seem to be an important promoter of regular spike activity in the small intestine. Psychological stress results in quantitative alterations in bacteria (7,8). Stressed mice exhibit a decrease in the relative proportion of *Lactobacilli* and *Escherichia coli*, changes that could be related to small intestine dysfunction (7). Qualitative and quantitative changes in gut flora have been described in patients with IBS. A study of fecal samples has shown qualitative differences between healthy controls and IBS patients and between IBS patients with constipation or diarrhea predominant. The study showed that although patients with constipation-predominant IBS had higher concentrations of *Veillonella* spp, patients with diarrhea-predominant IBS had lower levels of *Lactobacillus* spp. Galatola et al found evidence of bacterial overgrowth in 56% diarrhea-predominant IBS and 28% of the constipation-predominant type (9). Pimentel et al have found bacterial overgrowth in 78% of patients with IBS (10). Changes in gut flora, resulting from the use of antibiotics, have also been proposed as a pathogenic mechanism of IBS. Studies have shown that patients who received antibiotics in the previous months were approximately 3 times more likely than patients who did not receive antibiotics to develop functional symptoms (11,12). Probiotics and antibiotics have also been used to treat a proposed dysfunctional relation between the indigenous flora and the host in patients with IBS (10,13–15). Verdu et al suggest a possible pathogenic mechanism linking changes in flora and IBS (16). Perturbations in gut flora and inflammatory cell activity may modify the sensory neurotransmitter content in the colon, leading to altered visceral perception, dysmotility, increased gas production, and changes in bowel habits. Increased numbers of inflammatory cells in the lamina propria, proximity of mast cells to nerves, and production of substances that activate receptors involved in visceral sensation have been shown in patients with IBS (17).

Pathogenic bacteria leading to acute gastroenteritis may also cause persistent GI symptoms and FGIDs including IBS (18) and dyspepsia (19). Postinfectious IBS develops in 10% to 34% of adult patients following acute infectious enteritis (20). A multicenter controlled study conducted by our group has recently demonstrated the presence of postinfectious IBS in children (21). This study showed a significant increase in prevalence of abdominal pain in patients experiencing acute gastroenteritis of bacterial origin several years after the initial episode subsided. Although the pathogenesis of postinfectious IBS remains unclear, some authors propose that changes in gut mucosal function and structure, increased mucosal permeability, infiltration of enteroendocrine cells, and persistent neuroimmune interactions leading to continuing sensorimotor dysfunction could explain this phenomenon (22).

The different organ systems also live in an integrated equilibrium with each other. The enteric nervous system has a bidirectional dialogue with the brain via parasympathetic and sympathetic pathways that integrate the brain–gut axis. Stress, defined as an acute threat to homeostasis, may lead to intestinal inflammation, increased intestinal permeability, visceral hypersensitivity, and dysmotility (23). Psychological and physical stressors may be involved in the onset and modulation of IBS symptoms. Stress can lead to mast cell activation, degranulation (24), and release of mediators that alter the gut motor response and visceral perception through its effect on enteric neurons and smooth muscle cells. Mast cells may constitute the final pathway of various mechanisms sensitizing the GI tract such as stress, food allergies, and infections (25). School-related stress may play a role in explaining the seasonal variation of abdominal pain and other somatic complaints described in healthy children at the community level and in consultations for abdominal pain (26). Three independent pediatric studies conducted in different settings have concluded that there is a higher prevalence of complaints and consultations for abdominal pain during winter months in comparison with summer months (26–28). However, the analysis of the monthly pattern of gastrointestinal complaints in different schools and cities showed that those complaints do not occur during the whole school year, whereas school-related stress should

be present during the entire academic year. The presence of a significant decrease in somatic complaints at the end of winter and beginning of spring suggests a possible involvement of factors other than school stress. Minor or subclinical infections in certain months of the year could play a role in this seasonal pattern. A decreased ability to cope was described in children with recurrent abdominal pain (29). A study suggested different seasonal patterns of abdominal pain in children living in different latitudes (30). Limitations in outside activities due to weather conditions may result in a decreased ability to cope through play during certain months of the year.

The possible effect of hormones with an important environmental underpinning should also be considered. Melatonin production illustrates the integration between ecosystems and organ systems. Melatonin, initially thought to be found only in the pineal gland, was then shown to be present in a much greater concentration in the gut, mainly in the enterochromaffin cells. Melatonin serum levels vary according to the daylight cycle and weather (external ecosystem). Melatonin is also produced by the gut flora and its intestinal concentration is modulated by meals (internal ecosystem). Multiple studies have shown an important effect of melatonin on gastrointestinal function (31). Melatonin affects GI circadian entrainment, has antioxidant and cytoprotective activity, and anti-inflammatory effects. Melatonin also regulates gut motility and sensation, important factors in the pathogenesis of IBS (32). Multiple clinical trials have shown a beneficial role of melatonin in the treatment of IBS (33) and dyspepsia even in the absence of sleep disturbances (34). Melatonin has also been implicated in the treatment and pathogenesis of headaches (35), a common comorbidity in children with abdominal pain (36). Headaches and IBS share the biopsychosocial model (36). The evidence derived from these studies, the physiological implications of melatonin on the GI tract, and the presence of feedback mechanism between melatonin and serotonin justifies further investigation on the effects of this hormone on the GI tract and its possible role in the treatment of FGIDs (33,37).

In summary, health, illness, and the various phenotypic expressions of each condition may be viewed as the results of multiple internal and external factors interacting and mutually affecting each other. We should be open to explore novel factors that could advance our understanding of the pathogenesis of FGIDs.

REFERENCES

1. Drossman DA. Gastrointestinal illness and the biopsychosocial model. *J Clin Gastroenterol* 1996;22:252–4.
2. Whorwell P, Lea R. Dietary treatment of the irritable bowel syndrome. *Curr Treat Options Gastroenterol* 2004;7:307–16.
3. Atkinson W, Sheldon TA, Shaath N, et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004;53:1459–64.
4. Zar S, Mincher L, Benson MJ, et al. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol* 2005;40:800–7.
5. Camilleri M. Probiotics and irritable bowel syndrome. rationale, putative mechanisms, and evidence of clinical efficacy. *J Clin Gastroenterol* 2006;40:264–9.
6. Husebye E, Hellstrom PM, Sundler F, et al. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. *Am J Physiol* 2001;280:G368–80.
7. Holdeman LV, Good IJ, Moore WE. Human fecal flora. Variation in bacterial composition within individuals and a possible effect of emotional stress. *Appl Environ Microbiol* 1976;31:359–75.
8. Wang SX, Wu WC. Effects of psychological stress on small intestinal motility and bacteria and mucosa in mice. *World J Gastroenterol* 2005;11:2016–21.
9. Galatola G, Grosso M, Barlotta A, et al. Diagnosis of bacterial contamination of the small intestine using the 1 g [14C] xylose breath test in various gastrointestinal diseases. *Min Gastroenterol Dietol* 1991;37:169–75.
10. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome. a randomized trial. *Ann Intern Med* 2006;145:557–63.
11. Mendall MA, Kumar D. Antibiotic use, childhood affluence and irritable bowel syndrome (IBS). *Eur J Gastroenterol Hepatol* 1998;10:59–62.
12. Maxwell PR, Rink E, Kumar D, et al. Antibiotics increase functional abdominal symptoms. *Am J Gastroenterol* 2002;97:104–8.
13. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL#3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil* 2005;17:687–96.
14. Quigley EM, Flourie B. Probiotics and irritable bowel syndrome. A rationale for their use and an assessment of the evidence to date. *Neurogastroenterol Motil* 2007;19:166–72.
15. Sharara AI, Aoun E, Abdul-Baki H, et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol* 2006;101:326–33.
16. Verdu EF, Bercik P, Verma-Gandhu M, et al. Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. *Gut* 2006;55:182–90.
17. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126:693–702.
18. Gwee KA, Collins SM, Read NW, et al. Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. *Gut* 2003;52:523–6.
19. Mearin F, Perez-Oliveras M, Perello A, et al. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak. One-year follow-up cohort study. *Gastroenterology* 2005;129:98–104.
20. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003;124:1662–71.
21. Saps M, Pensabene L, Di Martino L, et al. Post-infectious functional gastrointestinal disorders in children. *J Pediatr* 2008;152:812–6.
22. Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 2000;47:804–11.
23. Hart A, Kamm MA. Review article. mechanisms of initiation and perpetuation of gut inflammation by stress. *Aliment Pharmacol Ther* 2002;16:2017–28.
24. Bhatia V, Tandon RK. Stress and the gastrointestinal tract. *J Gastroenterol Hepatol* 2005;20:332–9.
25. Wood JD. Effects of bacteria on the enteric nervous system. Implications for the irritable bowel syndrome. *J Clin Gastroenterol* 2007;41:S7–19.

26. Saps M, Blank C, Khan S, et al. Seasonal variation in the presentation of abdominal pain. *J Pediatr Gastroenterol Nutr* 2008;46:279–84.
27. MacIver R, Mears C, Di Lorenzo C, et al. Seasonal nurse consultations for abdominal pain in an adolescent population. *J Pediatr Gastroenterol Nutr* 2007;45:E13.
28. Saps M, Di Lorenzo C. An epidemiological study of common GI symptoms in school-age children. *Gastroenterology* 2007;132:A–325.
29. Thomsen AH, Compas BE, Colletti RB, et al. Parent reports of coping and stress responses in children with recurrent abdominal pain. *J Pediatr Psychol* 2002;27:215–26.
30. Saps M, Sztainberg M, Di Lorenzo C. A prospective community-based study of gastroenterological symptoms in school-age children. *J Pediatr Gastroenterol Nutr* 2006;43:477–82.
31. Konturek SJ, Konturek PC, Brzozowska I, et al. Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). *J Physiol Pharmacol* 2007;58: 381–405.
32. Bubenik GA. Gastrointestinal melatonin. localization, function, and clinical relevance. *Dig Dis Sci* 2002;47:2336–48.
33. Song GH, Leng PH, Gwee KA, et al. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances. A randomised, double blind, placebo controlled study. *Gut* 2005;54:1402–7.
34. Lu WZ, Gwee KA, Moochhalla S, et al. Melatonin improves bowel symptoms in female patients with irritable bowel syndrome. A double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2005;22:927–34.
35. Peres MF, Masruha MR, Zukerman E, et al. Potential therapeutic use of melatonin in migraine and other headache disorders. *Expert Opin Invest Drugs* 2006;15:367–75.
36. Levy RL, Olden KW, Naliboff BD, et al. Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology* 2006;130: 1447–58.
37. Elsenbruch S. Melatonin. A novel treatment for IBS? *Gut* 2005;54:1353–4.

Psychological Factors in the Development and Natural History of Functional Gastrointestinal Disorders

Lynn S. Walker

Director, Division of Adolescent Medicine and Behavioral Science, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN

The theory of stress and coping proposed by Lazarus and Folkman (1) is useful in understanding why some children adapt to functional gastrointestinal disorders (FGIDs) and others become increasingly incapacitated. In applying this theory to FGIDs, we make the assumption that abdominal pain is a stressor. According to Lazarus and Folkman, the personal meaning we attach to an event—in this case, an episode of abdominal pain—shapes our emotional and behavioral responses to the event. Given the same event, some people will anticipate harm, feel threatened, and try to escape the situation. Other people facing the same event will anticipate mastery, feel challenged, and take action to confront the situation. Applying this formulation of stress and coping to abdominal pain, we would expect that children's pain appraisals and coping strategies would contribute significantly to their course of illness. Indeed, our prospective study of pediatric patients with chronic abdominal pain showed that those who felt most threatened by pain used passive coping strategies and had poor outcomes, whereas those who accepted pain and used accommodative coping strategies had more positive outcomes (2). Thus, whether children's mastery efforts in confronting pain are negative, characterized by perceived threat and avoidance of situations associated with pain, or positive, characterized by perceived challenge and direct action, significantly influences their course of symptoms and disability.

At times of stress, people may rely both on their own mastery efforts and on their social network. Thus, it is not surprising that children's social relationships also influence the course of pediatric FGIDs (3–6). Interpersonal relationships associated with pain can be positive, characterized by support, or negative, characterized by isolation. Recent research shows that the quality of children's mastery efforts and interpersonal relationships define 4 profiles of children with chronic abdominal pain (7), as illustrated in Fig. 1.

Avoidant copers are characterized by poor pain mastery efforts and withdrawal from interpersonal relationships when dealing with pain. They view their abdominal pain as

Address correspondence and reprint requests to Lynn S. Walker, PhD, Adolescent Medicine and Behavioral Science, Vanderbilt Children's Hospital, 2200 Children's Way, Room 11128, Nashville, TN 37232-9060 (e-mail: lynn.walker@vanderbilt.edu).

Preparation of this article was supported by a grant from the National Institute of Child Health and Development (R01 HD23264).

The author reports no conflicts of interest.

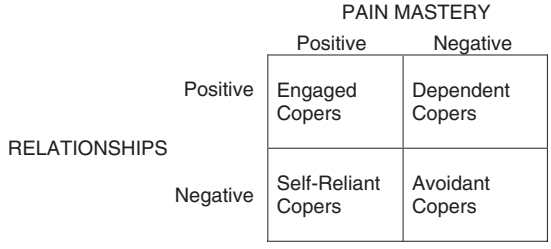

FIG. 1. Patient coping styles vary by pain mastery efforts and interpersonal relationships associated with pain.

serious and themselves as powerless. They avoid others and tend to be depressed and incapacitated by pain. Over time, their withdrawal from activities may lead to problems of academic and social adjustment.

Dependent copers are similar to avoidant copers in that they make little effort to master pain themselves. However, whereas avoidant copers withdraw from others, dependent copers seek social support. Indeed, their helplessness and catastrophizing about pain may elicit support from others that reinforces their disability. To the extent that they are incapacitated by pain, these children may fall behind their peers in academic and social domains.

Self-reliant copers are characterized by high pain mastery efforts and refusal of assistance or sympathy from others. These patients are stoic; they attempt to master pain without letting others know that they are suffering. Because they continue their activities, their social and academic adjustment is not affected by pain. Stoicism exacts an emotional cost (8), however, which is reflected in depressive symptoms in some of these patients.

Engaged copers are characterized by both positive mastery efforts and positive interpersonal relationships associated with pain. They engage in active problem solving and self-encouragement. In addition, they engage in social relationships and seek support in coping with pain, but are not dependent on others. These patients accommodate their pain and, as a consequence, continue to develop their social and academic competence. Of the 4 profile groups, engaged copers exhibit the most resilient, adaptive response to pain.

By assessing children's mastery efforts and interpersonal relationships associated with abdominal pain, practitioners can identify those who are likely to have poor outcomes and may need more extensive medical follow-up as well as referral to behavioral health providers.

REFERENCES

1. Lazarus RS, Folkman S. Stress, Appraisal, and Coping. New York: Springer; 1984.
2. Walker LS, Smith CA, Garber J, et al. Testing a model of pain appraisal and coping in children with recurrent abdominal pain. *Health Psychol* 2005;24:364–75.
3. Levy RL, Whitehead WE, Walker LS, et al. Increased somatic complaints and health care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastro* 2004;99:1–10.
4. Van Slyke DA, Walker LS. Mothers' responses to children's pain. *Clin J Pain* 2006;22:387–91.
5. Walker LS, Claar RL, Garber J. Social consequences of children's pain: when do they encourage symptom maintenance? *J Pediatr Psychol* 2002;27:689–98.
6. Walker LS, Williams SE, Smith CA, et al. Parent attention versus distraction: impact on symptom complaints by children with and without chronic functional abdominal pain. *Pain* 2006;122:43–52.
7. Walker LS, Baber KF, Garber J, et al. A typology of pain coping strategies in pediatric patients with chronic abdominal pain. *Pain* 2008;137:266–75.
8. Yong H. Can attitudes of stoicism and cautiousness explain observed age-related variation in levels of self-rated pain, mood disturbance and functional interference in chronic pain patients? *Eur J Pain* 2006;10:399–407.

Functional Abdominal Pain: The Basic Science

Jackie D. Wood

Professor of Physiology and Cell Biology and Internal Medicine, Ohio State University, College of Medicine, Columbus, OH

Primary causes of abdominal pain of digestive tract origin are distension and excessively strong contractions of the musculature. Other stimuli (eg, pinching and burning of the mucosa) do not evoke pain. Hypersensitivity of the mechanoreceptors, which detect stretch (ie, distension) and contractile force, is a pain factor in functional gastrointestinal disorders (FGIDs). Hypersensitivity to distension is found in a substantial subset of patients that meet Rome III symptom-based criteria for diagnosis of irritable bowel syndrome (IBS) (1–4).

Address correspondence and reprint requests to Prof Jackie D. Wood, MSc, PhD, 304 Hamilton Hall, 1645 Neil Ave, Columbus, OH 43210-1218 (e-mail: wood.13@osu.edu).

The author has received research grants from Novartis Pharmaceuticals and Sucampo Pharmaceuticals.

Inflation of a balloon placed in the rectosigmoid region evokes sensations of discomfort and pain at lower distending volumes for patients with IBS than for healthy subjects. Hypersensitivity to distension in these cases is not restricted to the distal large intestine. Patients with functional dyspepsia also experience discomfort and pain at lower distending volumes in the stomach that healthy individuals (4–6) and hypersensitivity to distension is present in the esophagus of patients with noncardiac chest pain (7).

Patients with IBS experience the same kind of hypersensitivity to electrical stimulation applied to the mucosa of the rectosigmoid region as they do during balloon distension in the rectosigmoid region (8). The hypersensitivity to direct electrical stimulation of the intramural sensory innervation implicates abnormal sensory neurophysiology rather than mechanical factors (eg, wall tension, compliance) as underlying the decreased sensory threshold in patients with IBS. Precise identification of the sensory defect in IBS is an area of active investigation and not yet satisfactorily established. In fact, the lower sensory threshold in IBS may reflect sensitization of intramural mechanoreceptors, sensitization of neurotransmission at synapses in the spinal cord, abnormal processing of the sensory information when it reaches the brain, and combinations of each of these possibilities.

PERIPHERAL NEUROPATHOLOGICAL FACTORS

Mechanosensitive primary sensory afferents in the walls of the specialized organs of the digestive tract detect and signal the strength and rate of change of contraction and distension of the musculature. The mechanosensitive structures expressed at the afferent terminals behave as if they are attached in series with the long axes of the smooth muscle fibers. This arrangement accounts for activation of the sensors by either muscle contraction or distension. The cell bodies of the neurons that give rise to gastrointestinal sensory afferents are located in vagal nodose ganglia and dorsal root spinal ganglia. Mechanosensitive information is transmitted along spinal afferents to the spinal cord by way of dorsal root ganglia and along vagal sensory afferents to the brainstem by way of the nodose ganglia and synaptic relays in the nucleus tractus solitarius.

Sensations of pain and discomfort of digestive tract origin reflect transmission in spinal afferents and information processing in the spinal cord and brain. Sensory information transmitted by the vagus nerves appears not to reach the level of conscious sensation because patients with high spinal cord transections and intact vagal pathways experience little or no sensations of digestive tract origin. Conscious perception of sensations from the digestive tract remains after a surgical vagotomy and, presumably, reflects transmission over spinal afferents to the spinal cord and onward to conscious centers in the brain.

The streams of mechanosensory information, which are transmitted from the small and large intestine to the central nervous system, are generated by 3 kinds of sensory afferents identified as low-threshold, high-threshold or silent afferents (9). Low-threshold afferents, which code for small changes in wall tension, are believed to transmit the minute-to-minute information required for functional autonomic negative-feedback control during contractile events. To be activated, high-threshold afferents require stronger changes in wall tension, which may be produced by distension of the lumen or strong contraction of the musculature. High-threshold afferents are postulated to be responsible for the range of sensations from mild to severe pain that are associated with excessive distension or exceptionally strong muscle contraction. Silent afferents cannot be activated by distension when the bowel is in its normal state. They acquire pathophysiological significance by becoming active and highly sensitive to stimuli during inflammatory states (10,11).

POSTINFECTIOUS IBS

A significant percentage of individuals develop IBS-like symptoms after an acute bout of infectious enteritis (12–15). The issue of whether the association between acute infectious enteritis and IBS reflects low-level inflammation (eg, microscopic enteritis) and chronic exposure of the neural and glial elements of the enteric nervous system to elevated levels of serotonin, histamine, or other inflammatory mediators remains to be fully resolved.

SEROTONIN RECEPTORS ON SENSORY AFFERENTS

Application of serotonin in animal studies evokes increased firing in sensory fibers leaving the stomach and small and large intestine and this is mediated by the serotonergic 5-HT_3 receptor subtype. Selective 5-HT_3 receptor antagonists (eg, alosetron) block this action (16,17). Intramural terminals of both spinal and vagal sensory nerves express 5-HT_3 receptors. Efficacy of alosetron in the treatment of abdominal pain and discomfort in the diarrhea-predominant form of IBS in women suggests that their symptoms may reflect overactive endogenous release and elevated levels of serotonin (18,19).

Persistence of serotonin at its receptors, due to weakened uptake by the serotonin transporter, is a second possibility for hyperstimulation of intramural serotoninergic receptors. Active uptake mediated by the serotonin transporter, which is expressed by enteric neurons and mucosal epithelial cells, normally restricts accumulation

and action of serotonin at its receptors following its release (20). Downregulation of gene expression for the serotonin transporter is reported to be present in mucosal biopsies taken from the large intestine of patients with IBS (21). Enhanced propulsive motility and watery stools occurred in mice with a deletion in the serotonin transporter gene, and Chen et al (22) reported that these mice sometimes alternate between diarrhea and constipation in ways reminiscent of the subset of patients with IBS, who are classified as alternators.

RECEPTORS FOR INFLAMMATORY MEDIATORS ON SENSORY AFFERENTS

Receptors for bradykinin, adenosine triphophate, adenosine, prostaglandins, leukotrienes, histamine and mast cell proteases, like 5-HT_3 receptors, are expressed on intramural spinal sensory nerve terminals (9,23). Any of these inflammatory cell-derived or ischemia-related mediators has potential for elevating the sensitivity of intestinal sensory nerves, especially in the disordered conditions of inflammation or ischemia. This likelihood is reinforced by findings that a reduced threshold for painful responses to balloon distension in the large intestine is associated with degranulation of enteric mast cells in animal models. Treatment with mast cell stabilizing drugs prevents the lowering of the pain threshold, which occurs during mucosal inflammation in the animal models (24), and suggests that mast cell stabilization may be an efficacious treatment in human IBS (25,26).

CENTRAL NEUROPATHOLOGICAL FACTORS

The evidence is consistent with altered peripheral sensory transduction as the underlying factor for the exaggerated sensitivity to distension found in patients with IBS (27). In this scenario, mechanosensitive primary afferents in the gut wall become hypersensitive to mechanical stimuli and as a result transmit at elevated frequencies of firing, which is then interpreted in the central nervous system as nociception. In an alternative scenario, normally functioning mechanoreceptors transmit accurate information, which is then misinterpreted in processing circuits in the spinal cord and/or brain to evoke conscious perceptions of disordered sensations from the gut.

ASCENDING SENSORY PATHWAYS IN THE SPINAL CORD

Ascending spinal pathways involved in the transmission of nociceptive signals from the digestive tract are the spinothalamic, spinohypothalamic, spinosolitary, spinoreticular, and spinoparabrachial tracts. Visceral pain information is also transmitted to higher processing centers in the brain along pathways in the dorsal spinal columns (28–30). Spinal afferents, which transmit nociceptive information, connect synaptically with second-order neurons in the dorsal column nuclei (ie, nucleus gracilis and nucleus cuneatus). Second-order neurons in the spinal dorsal horn also provide input to the dorsal column nuclei. The pain signals are transmitted cephalad by way of the ipsilateral dorsal column nuclei to the contralateral ventroposterolateral nucleus of the thalamus (28,30,31).

A midline myelotomy, which severs axons in the human dorsal columns, attenuates visceral pain that is otherwise intractable (31,32). Electrical stimulation of the dorsal columns in patients with severe IBS evokes an immediate increase in the intensity of their abdominal pain (33). These observations in humans are consistent with experimental results in animals (29,34).

SENSORY PROCESSING IN THE CEREBRAL CORTEX

Methods of brain imaging have emerged as a useful investigative tool for addressing questions related to abnormal processing of sensory information in the cerebral cortex of patients with FGID (27,35–37). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are methods commonly used to study information processing in the higher brain centers that underlie an individual's conscious experience of gut-related sensations.

Results from imaging studies suggest that unlike somatic sensation, which has a main homuncular representation in the primary somatosensory cortex, visceral sensation is mainly represented in the secondary somatosensory cortex (37,38). Differences in processing in these specialized regions may account for the imprecise nature of an individual's ability to localize visceral sensation in relation to somatic sensation. Beyond the sensory cortices, fMRI and PET images show representation of both somatic and visceral sensation to be similar in the limbic and paralimbic regions of the cortex (eg, anterior insular, anterior and posterior cingulate, prefrontal and orbitofrontal cortices (35,36). Activity in these areas underlies the individual's motivational and emotional mood and the cognitive aspects of visceral sensations.

Sex differences, reminiscent of the female predominance in IBS, are seen in the cortical representation when a balloon is distended in the rectosigmoid region in healthy subjects of both sexes (39). On the one hand, activation in the sensory/motor and parieto-occipital areas of the cortex does not differ for males and females. On the other hand, activation in the anterior cingulate and prefrontal cortices is more extensive in females than in males. Amounts of evoked cortical activity in females is greater than in males for perception levels in the range

from the urge to defecate to sensations of fullness, mild discomfort, and pain. Significance of these sex differences is unclear; nevertheless, they are reminiscent of the greater perceptual responses reported in female patients with FGIDs (eg, IBS) (40).

In healthy subjects, painful sensations evoked by distension of a balloon in the rectosigmoid region, as well as the anticipation of a potentially painful distension, are associated with increased blood flow in the anterior cingulate cortex in PET. In patients with IBS, activation of the anterior cingulate cortex occurs in response to painful distension or the anticipation of painful distension (35,41). A different study with fMRI found that patients with IBS showed enhanced activation of the mid-cingulate cortex in response to rectal distension (42). The cingulate cortex has become a focus of attention because it is generally thought to be an integrative center for both emotional experience and pain-specific sensory information that may account for the well-known linkage between pain and the individual's emotional state. The so-called affective areas of the cingulate cortex have extensive connections with the amygdala and periaqueductal gray matter and with autonomic nuclei in the brainstem (43). Activity in these connections integrates recall of emotional experiences with neural autonomic and endocrine control functions at the level of the gut. Cognition is believed to reside in the caudal portion of the anterior cingulate cortex where the microcircuits are delegated to premotor functions and processing of nociceptive information.

The functional neuroanatomy of the cingulate cortex offers an explanation for the well-documented association of psychosocial disturbances (eg, negative life events) with more severe cases of IBS (40). Rectal distension in people with histories of severe sexual and/or physical abuse has been reported to selectively activate the perigenual region of the anterior cingulate cortex. A case report described a middle-age female whose low pain threshold for rectal distension and diarrhea-predominant IBS improved after she was extricated from an abusive psychosocial situation. Brain imaging with fMRI in this individual showed activation of the mid-cingulate cortex during rectal distension before treatment and resolution of activation associated with improvement in the patient's psychosocial situation (44).

CENTRAL SENSITIZATION (''WIND UP'')

Elevated excitability in nociceptive dorsal horn neurons underlies spinally mediated hyperalgesia, which is called central sensitization to distinguish it from sensitization that occurs at nociceptive terminals in the periphery. In conditions of severe tissue injury and persistent injury, nociceptive C fibers fire repetitively and the excitability of the second-order neurons in the dorsal horn increases progressively in response to the elevated synaptic input. This effect is sometimes called wind-up and reflects the synaptic release of glutamate from the incoming C-fibers and activation of *N*-methyl-D-aspartate-type glutamate receptors expressed by the second-order neurons. These long-lasting changes in the excitability of dorsal horn neurons are like a memory imprint of the nociceptive input. Accumulating evidence suggests that the spinal wind up phenomenon is operational for the intestinal tract and may be an underlying factor in the hypersensitivity associated with IBS.

Suggestive evidence for wind up hypersensitivity is the finding that second-order neurons in the dorsal horn show induction of the early gene *c-fos* in response to noxious balloon distension of the colon in rats (45). Changes in gene expression in this case are expected to underlie postsynaptic excitability changes in the second-order nociceptive neurons. A related phenomenon occurs in the rat spinal cord where excitability of second-order nociceptive neurons becomes sensitized to distension-evoked input following inflammation of the colon. The same phenomenon is evident in dorsal column nuclei where firing of second-order neurons to colorectal distension becomes sensitized following inflammation of the colonic mucosa (46).

In a study, which is reminiscent of the connection between sexual and physical abuse documented for early childhood and IBS in adult humans, Al-Chaer et al (47) reported that central sensitization may also be induced in animal models in the absence of inflammation. Neonatal rats in their study were subjected daily to noxious colorectal distension or intracolonic injection of mustard oil beginning 8 days postpartum and lasting for 21 days. When tested in adulthood, the rats that were ''abused'' as neonates were hypersensitive to colorectal distension as reflected by a lower threshold and elevated intensity of reflex responses indicative of abdominal pain. Single-unit electrophysiological recording from dorsal horn neurons in the lumbar and sacral regions of the spinal cord of the adult animals detected significantly higher background firing frequencies in the animals that were abused as neonates and enhanced firing frequencies in response to colorectal distension when compared with nonabused controls. Histological examination uncovered no evidence of an inflammatory state in the large intestine in either the adult abused animals or their controls in these studies.

Limited evidence for central sensitization to distension of the large bowel has been obtained for humans who meet Rome II or III diagnostic criteria for IBS (3). In this group of patients, repetitive inflation of a balloon in the sigmoid colon to noxious levels of stimulation altered the processing of afferent information entering the spinal cord from the rectum. Altered central processing was present in the patients with IBS and not in healthy controls.

INTESTINAL MOTILITY AND ABDOMINAL PAIN

Strong contractions of the intestinal circular muscle coat during intestinal power propulsion underlie the sensation of cramping abdominal pain (48,49). Power propulsion occurs more frequently in patients with IBS than in healthy subjects, and the circular muscle contractions are significantly stronger than normal in patients with IBS (50). Moreover, postprandial power propulsion is more prevalent in the colons of patients with IBS than in normal individuals and power propulsion in the colon is often associated with their diarrheal state (51). The pain and discomfort in patients with IBS during the powerful contractions of power propulsion may be explained in 3 ways, either separately or in combination. One explanation is for the exceptionally powerful circular muscle contractions to activate high-threshold mechanoreceptors that transmit the information centrally, where it is processed and projected to consciousness as the perception of pain and discomfort. A second is for the mechanoreceptors to become sensitized in the patients with IBS (eg, by inflammatory mediators or other paracrine signals) and send erroneously coded information to processing centers in the spinal cord and brain. A third explanation is for accurately coded sensory information carried by spinal afferents to be misinterpreted as it is decoded in the spinal cord and central processing centers of the brain.

Acknowledgment: The author thanks the National Institutes of Health NIDDK Institute for support of work on enteric neurobiology since 1973.

REFERENCES

1. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. *Gut* 1973;14:125–32.
2. Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 1990;98:1187–92.
3. Munakata J, Naliboff B, Harraf F, et al. Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. *Gastroenterology* 1997;112:55–63.
4. Chang L, Munakata J, Mayer EA, et al. Perceptual responses in patients with inflammatory and functional bowel disease. *Gut* 2000;47:497–505.
5. Camilleri M, Coulie B, Tack JF. Visceral hypersensitivity: facts, speculations, and challenges. *Gut* 2001;48:125–31.
6. Bouin M, Lupien F, Riberdy-Poitras M, et al. Tolerance to gastric distension in patients with functional dyspepsia: modulation by a cholinergic and nitrergic method. *Eur J Gastroenterol Hepatol* 2006;18:63–8.
7. Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91: 845–52.
8. Rossel P, Drewes AM, Petersen P, et al. Pain produced by electric stimulation of the rectum in patients with irritable bowel syndrome: further evidence of visceral hyperalgesia. *Scand J Gastroenterol* 1999;34:1001–6.
9. Beyak MJ, Bulmer DCE, Jiang W, et al. Estrinsic sensory afferent nerves innervating the gastrointestinal tract. In: Johnson LR, Barrett KE, Ghishan FK (eds). *Physiology of the Gastrointestinal Tract.* 4th ed.. et al. San Diego: Academic Press; 2006. pp. 685–725.
10. Ness TJ, Gebhart GF. Acute inflammation differentially alters the activity of two classes of rat spinal visceral nociceptive neurons. *Neurosci Lett* 2000;281:131–4.
11. Xu GY, Huang LY, Zhao ZQ. Activation of silent mechanoreceptive cat C and A-delta sensory neurons and their substance P expression following peripheral inflammation. *J Physiol* 2000;528 (Pt 2):339–48.
12. Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;44:400–6.
13. Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. *Gut* 2004;53:1096–101.
14. Collins SM, Barbara G. East meets West: infection, nerves, and mast cells in the irritable bowel syndrome. *Gut* 2004;53:1068–9.
15. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003;124:1662–71.
16. Hillsley K, Kirkup AJ, Grundy D. Direct and indirect actions of 5-hydroxytryptamine on the discharge of mesenteric afferent fibres innervating the rat jejunum. *J Physiol* 1998;506 (Pt 2):551–61.
17. Kozlowski CM, Green A, Grundy D, et al. The 5-HT(3) receptor antagonist alosetron inhibits the colorectal distention induced depressor response and spinal c-fos expression in the anaesthetised rat. *Gut* 2000;46:474–80.
18. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med* 2001;161:1733–40.
19. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. *Aliment Pharmacol Ther* 1999;13:1149–59.
20. Chen JX, Pan H, Rothman TP, et al. Guinea pig 5-HT transporter: cloning, expression, distribution, and function in intestinal sensory reception. *Am J Physiol* 1998;275:G433–48.
21. Coates MD, Mahoney CR, Linden DR, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004;126:1657–64.
22. Chen JJ, Li Z, Pan H, et al. 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. *J Neurosci* 2001;21:6348–61.
23. Kirkup AJ, Brunsden AM, Grundy D. Receptors and transmission in the brain-gut axis: potential for novel therapies. I. Receptors on visceral afferents. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G787–94.
24. Coelho AM, Fioramonti J, Bueno L. Mast cell degranulation induces delayed rectal allodynia in rats: role of histamine and 5-HT. *Dig Dis Sci* 1998;43:727–37.
25. Siddiqui AA, Miner PB Jr. The role of mast cells in common gastrointestinal diseases. *Curr Allergy Asthma Rep* 2004;4:47–54.
26. Santos J, Alonzo C, Guilarte M, et al. Targeting mast cells in the treatment of functional gastrointestinal disorders. *Curr Opin Pharmacol* 2006;6:541–6.
27. Lawal A, Kern M, Sidhu H, et al. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. *Gastroenterology* 2006;130:26–33.
28. Al-Chaer ED, Lawand NB, Westlund KN, et al. Visceral nociceptive input into the ventral posterolateral nucleus of the thalamus: a new function for the dorsal column pathway. *J Neurophysiol* 1996;76:2661–74.
29. Al-Chaer ED, Feng Y, Willis WD. A role for the dorsal column in nociceptive visceral input into the thalamus of primates. *J Neurophysiol* 1998;79:3143–50.

30. Ness TJ. Evidence for ascending visceral nociceptive information in the dorsal midline and lateral spinal cord. *Pain* 2000;87:83–8.
31. Kim YS, Kwon SJ. High thoracic midline dorsal column myelotomy for severe visceral pain due to advanced stomach cancer. *Neurosurgery* 2000;46:85–90.
32. Hirshberg RM, Al-Chaer ED, Lawand NB, et al. Is there a pathway in the posterior funiculus that signals visceral pain? *Pain* 1996;67:291–305.
33. Malcolm A, Phillips SF, Kellow JE, et al. Direct clinical evidence for spinal hyperalgesia in a patient with irritable bowel syndrome. *Am J Gastroenterol* 2001;96:2427–31.
34. Al-Chaer ED, Lawand NB, Westlund KN, et al. Pelvic visceral input into the nucleus gracilis is largely mediated by the postsynaptic dorsal column pathway. *J Neurophysiol* 1996;76:2675–90.
35. Silverman DH, Munakata JA, Ennes H, et al. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology* 1997;112:64–72.
36. Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000;118: 842–8.
37. Hobday DI, Aziz Q, Thacker N, et al. A study of the cortical processing of ano-rectal sensation using functional MRI. *Brain* 2001;124:361–8.
38. Ladabaum U, Minoshima S, Hasler WL, et al. Gastric distention correlates with activation of multiple cortical and subcortical regions. *Gastroenterology* 2001;120:369–76.
39. Kern MK, Jaradeh S, Arndorfer RC, et al. Gender differences in cortical representation of rectal distension in healthy humans. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G1512–23.
40. Drossman DA, Creed FH, Olden KW, et al. Psychosocial aspects of the functional gastrointestinal disorders. *Gut* 1999;45:I25–30.
41. Ringel Y, Drossman DA, Turkington TG, et al. Regional brain activation in response to rectal distension in patients with irritable bowel syndrome and the effect of a history of abuse. *Dig Dis Sci* 2003;48:1774–81.
42. Naliboff BD, Derbyshire SW, Munakata J, et al. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. *Psychosom Med* 2001;63:365–75.
43. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain* 1995;118:279–306.
44. Drossman DA, Ringel Y, Vogt BA, et al. Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe irritable bowel syndrome. *Gastroenterology* 2003;124:754–61.
45. Traub RJ, Pechman P, Iadarola MJ, et al. Fos-like proteins in the lumbosacral spinal cord following noxious and non-noxious colorectal distention in the rat. *Pain* 1992;49:393–403.
46. Al-Chaer ED, Westlund KN, Willis WD. Sensitization of postsynaptic dorsal column neuronal responses by colon inflammation. *Neuroreport* 1997;8:3267–73.
47. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 2000;119:1276–85.
48. Wood JD, Alpers DH, Andrews PL. Fundamentals of neurogastroenterology. *Gut* 1999;45:II6–16.
49. Kamath PS, Phillips SF, O'Connor MK, et al. Colonic capacitance and transit in man: modulation by luminal contents and drugs. *Gut* 1990;31:443–9.
50. Chey WY, Jin HO, Lee MH, et al. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. *Am J Gastroenterol* 2001;96: 1499–506.
51. Wood JD. Enteric neuroimmunophysiology and pathophysiology. *Gastroenterology* 2004;127:635–57.

Amplified Musculoskeletal Pain: Treatment Approach and Outcomes

David D. Sherry

Director of Clinical Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA

In the past 2 decades and 1400 children with various forms of amplified musculoskeletal pain, I have seen a wide spectrum of this illness including complex regional pain syndrome, localized and diffuse amplified musculoskeletal pain, and fibromyalgia (a term I eschew). Our interdisciplinary team has developed a successful treatment program. Although having a team is helpful and necessary for some children, an individual practitioner may help many in their own community by paying attention and applying the various elements of our team. The mainstays of therapy are focusing on re-establishing function without medication or the use of modalities and addressing the psychological stress (1). Ultimately it is the child who works through his or her pain. The treatment starts at the first visit with confirming the diagnosis, discontinuing further medical evaluations, stopping

Address correspondence and reprint requests to David Sherry, MD, Children's Hospital of Philadelphia, Division of Rheumatology, 3405 Civic Center Blvd, Room 236, Seashore House, Philadelphia, PA 19104 (e-mail: sherry@email.chop.edu).

The author reports no conflicts of interest.

medications for pain (these 2 steps are sometimes much harder on the doctor than the child), and giving the child and family a working model of pain amplification to make the pain understandable (2). Confidence in both the diagnosis and treatment is paramount. The treatment is a team effort, although there are many children who, once they know what they have and how to treat it, can work through the pain without a formal intensive therapy program.

The formal intensive program at the Children's Hospital of Philadelphia includes physical therapy, occupational therapy, psychology, music therapy, school evaluation, and nursing, and on average lasts 3 to 4 weeks. Each has a role and each may be more or less important depending on the individual situation. The children receive 5 to 6 hours of one-to-one physical and occupational therapy. This is rigorous and focuses on function and desensitization (most children have allodynia) (3). We focus on doing what the children find the most difficult. We rapidly advance the difficulty of the exercises until they are functioning normally. The psychologist evaluates each child. It is critical that the experience of sitting down and talking about one's feelings is nonthreatening and even an enjoyable experience. When indicated, the psychologist will perform various psychological and educational tests. Music therapy is a place to connect to the body through relaxation with music, deal with sleep issues (we do not treat sleep with medication), and express oneself through music. Frequently this is the child's favorite aspect of the program because it can be the most nonthreatening place to talk about his or her feelings. The school educator receives information from the school about how the child functions academically and socially and helps smooth the reentry to school after the child graduates from the intense program. The second phase of our program is helping the child to maintain normal function, especially going to school, counseling (for most, depending on the evaluation), and doing a home exercise program on his or her own. The school educator, along with the psychologist, will not infrequently assess academic performance, strengths, and weaknesses and make specific school recommendations. The nurse assesses various somatic complaints, such as difficulty breathing, but with the bias that most symptoms are part of the child's tendency to feel emotions through his or her body. Most children fully participate in the program if they develop vomiting, minor illness and injuries, and most other somatic complaints.

It is important that the team is confident in its ability to cure these children, tolerate the child's pain, be genuinely interested in these children, and understand each other's roles and positions because both the child and parents are prone to try to split the team by playing one member off another.

Using this approach we have been successful in curing (ie, total resolution of symptoms) the vast majority of these children (4–6). In our study of complex regional pain syndrome, 95 of 103 were cured (4). The relapse rate was much lower than studies that used drug treatment (4,7); we believe this is, in large part, because our patients did the exercises themselves and thus cured themselves. If we fixed them with special modalities or medications, we fear the tendency would be for them to relapse and make it our job, not theirs, to fix them again. We have treated children with abdominal pain who are incapacitated or had marked allodynia of the abdomen and have been equally successful, although we have no long-term follow-up. Any outcome data should include other stress-related outcome data because we treat numerous children who go on to develop eating disorders, conversion reactions, attempt suicide, and other bodily pains (1,8–10).

These children and their families are rewarding to treat. We can help these children in the short term by helping them work through their pain and reestablish normal function, and we can help these children and their families in the long term by addressing the underlying psychological issues so that they cope with stress in a much more healthy fashion.

REFERENCES

1. Sherry DD. Pain syndromes. In: Miller JJI (ed). *Adolescent Rheumatology.* London: Martin Duntz, Ltd; 1998. pp. 197–227.
2. Sherry DD. An overview of amplified musculoskeletal pain syndromes. *J Rheumatol* 2000;27 (Suppl 58):44–8.
3. Sherry DD. *Amplified Musculoskeletal Pain in Children: Diagnosis and Treatment. A Guide for Physical & Occupational Therapists* (video). Wilmington, DE: Childhood RND Educational Foundation; 2002. *www.childhoodrnd.org*. Accessed August 15, 2008.
4. Sherry DD, Wallace CA, Kelley C, et al. Short- and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. *Clin J Pain* 1999;15:218–23.
5. Sherry DD, McGuire T, Mellins E, et al. Psychosomatic musculoskeletal pain in childhood: clinical and psychological analyses of 100 children. *Pediatrics* 1991;88:1093–9.
6. Sherry DD, Wallace CA. Resolution of fibromyalgia with an intensive exercise program (abstract). *Clin Exp Rheumatol* 1992;10:196.
7. Rabinovich CE, Schanberg LE, Stein LD, et al. A follow up study of pediatric fibromyalgia patients [abstract]. *Arthritis Rheum* 1990;33: S146.
8. Jaworowski S, Allen RC, Finkelstein E. Reflex sympathetic dystrophy in a 12-year-old twin with comorbid conversion disorder in both twins. *J Paediatr Child Health* 1998;34:581–3.
9. Silber TJ. Anorexia nervosa and reflex sympathetic dystrophy syndrome. *Psychosomatics* 1989;30:108–11.
10. Mikkelsson M, Sourander A, Piha J, et al. Psychiatric symptoms in preadolescents with musculoskeletal pain and fibromyalgia. *Pediatrics* 1997;100 (2 Pt 1):220–7.

The "4-1-1" on Migraine in Children and Adolescents

Ann Pakalnis

Director, Headache Clinic, Nationwide Children's Hospital, Columbus, OH

Migraine headaches are a common occurrence in children and adolescents. The prevalence ranges between 8% and 20%, with the highest frequency in adolescent girls. This figure is similar to the prevalence of migraines in the US adult population (1,2). Migraine is more common in boys in the pediatric population and more prevalent in women in the adult population. Frequent migraine attacks in children can be disruptive because they interfere with school and social activities and negatively affect parents' schedules by their having to care for an ill child.

CLASSIFICATION CRITERIA

Diagnosis of migraine is historical and based on guideline and objective criteria developed by the International Headache Society Classification Subcommittee (3). These criteria, also known as the International Classification of Headache Disorders II were last revised in 2004 and are the basis for the clinical diagnosis of headache disorders (Table 1). These criteria add credibility to the field of study of headache medicine and affect consensus in diagnosis around the world along with criteria used by the National Institutes of Health and the World Health Organization.

PATHOPHYSIOLOGY AND GENETICS OF MIGRAINES

Migraines are thought to be related to a complex interaction of primarily neurogenic activity in the spinal trigeminal nucleus in the brainstem and secondary release of vasoactive substances inducing a vasogenic inflammatory process that mediates the migraine symptom complex of nausea, vomiting, photophobia, and phonophobia. This interaction also causes the classic characteristic throbbing pain exacerbated by physical activity (4). The vasoactive substances involved are thought to include serotonin, substance P, and calcitonin gene-related peptide, among others. There is a strong genetic component to migraine, with prominence seen in familial clusters and the recent finding of a distinct familial hemiplegic migraine syndrome with gene mapping to chromosome 19 (5).

Address correspondence and reprint requests to Ann Pakalnis, MD, Nationwide Children's Hospital, Division of Neurology, 700 Children's Dr, Columbus, OH 43205 (e-mail: Ann.Pakalnis@nationwidechildrens.org).

The author reports no conflicts of interest.

COMORBIDITIES WITH PEDIATRIC MIGRAINE

Migraine frequency and severity is influenced by many environmental or lifestyle factors. Dehydration exacerbates migraines with its effects on central serotonin levels. Stress and emotional issues are well-known factors influencing headaches. Sleep dysfunction also negatively affects migraines. Several studies have delineated sleep abnormalities in pediatric migraineurs (6,7). Sleep-onset delays, daytime sleepiness, parasomnias, and nightmares are thought to be more common in children with migraine than in children without migraine. In addition, headache frequency and severity appear to be affected negatively by sleep dysfunction. Also, when assessing behavioral problems in patients

TABLE 1. *International criteria for headache diagnosis (ICHD-II)*

Pediatric migraine without aura
(A) More than 5 attacks fulfilling features B through D
(B) Headache attack lasting 1–72 h
(C) Headache has at least 2 of the following 4 features
Either bilateral or unilateral (frontal/temporal) location
Pulsating quality
Moderate to severe intensity
(D) A least 1 of the following accompanies headache
Nausea and/or vomiting
Photophobia and phonophobia (may be inferred from behavior)
Migraine with aura
(A) At least 2 attacks fulfilling criteria (B)
(B) Aura consisting of at least 1 of the following, but no motor weakness
Fully reversible visual symptoms including positive features
Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
Fully reversible dysphasic speech
(C) At least 2 of the following:
Homonymous visual symptoms and/or unilateral sensory symptoms
At least 1 aura symptom develops gradually over 5 min and/or different symptoms occur in succession over 5 min
Headache begins during the aura or follows within 60 min

with migraine, sleep disturbances correlated positively with behavioral issues (8).

Psychiatric and behavioral disorders are also more prevalent in children and adolescents with migraine. These disorders have included depression, anxiety, dysthymia, and oppositional defiant disorders (9,10). Psychiatric comorbidities can have a negative influence on treatment of migraine and compound pharmacological therapeutic choices. Long-term prognosis regarding headache disorders also may be influenced by psychological issues.

Primary headaches such as migraines are also associated with similar triggers and comorbidities such as those found in children with functional abdominal pain (10). Galli et al studied 70 children with headache, 70 patients with chronic or recurrent abdominal pain, and 70 healthy controls by using the Child Behavior Checklist, a parent rating scale for emotional and behavioral disorders (11). Anxiety, depression, somatization complaints, and internalizing behavioral issues occurred commonly in patients with these disorders. The presence of attention issues were the only difference between children with migraines and those with recurrent abdominal pain when studied using the Child Behavior Checklist.

SUMMARY

Migraine is common in the pediatric population. Lifestyle issues, stressors, sleep dysfunction, and psychiatric comorbidities are notable factors influencing migraine progression in children. These occurrences may have a negative effect on treatment success and are important issues to address. Psychological interventions to address these factors may be an important therapeutic option.

REFERENCES

1. Abu-Arefeh I, Russel G. Prevalence of headache and migraines in school children. *BMJ* 1994;309:765–9.
2. Stewart WF, Lipton RB, Celentano DD, et al. Prevalence of migraine headache in the United States. *JAMA* 1992; 267:64–9.
3. Headache Classifications Subcommittee of the International Headache Society. The International Classification of Headache Disorders. *Cephalalgia* 2004;24(Suppl 1):24–36.
4. Welch KM, Cutrer FM, Goadsby PJ. Migraine pathogenesis: neural and vascular mechanism. *Neurology* 2003;60 (Suppl 2):S9–14.
5. Ferrari MD. Heritability of migraine: genetic findings. *Neurology* 2003;60 (Suppl 2):515–20.
6. Heng K, Wirrell E. Sleep disturbance in children with migraine. *J Child Neurol* 2006;21:761–6.
7. Miller VA, Palermo TM, Powers SW, et al. Migraine headaches and sleep disturbances in children. *Headache* 2003;43:362–8.
8. Burnsztein C, Steinberg T. Sleep, sleepiness, and behavior problems in children with headache. *J Child Neurol* 2006;12: 1012–9.
9. Guidetti V, Gali FT, Fabrizi P, et al. Headache and psychiatric comorbidity: clinical aspects and outcome in an 8 year follow-up study. *Cephalagia* 1998;18:455–62.
10. Pakalnis A, Gibson J, Colvin A. Co-morbidity of psychiatric and behavioral disorders in pediatric migraine. *Headache* 2005;45: 590–6.
11. Galli F, D'Antuono G, Tarantino S, et al. Headache and recurrent abdominal pain: a controlled study by the means of the Child Behavioral Checklist (CBCL). *Cephalalgia* 2007;27: 211–9.

Orthostasis, the Autonomic Nervous System, and Abdominal Pain in Children: Is There a Relation Between Postural Orthostatic Tachycardia and Recurrent Abdominal Pain?

Mark E. Alexander

Associate in Cardiology, Arrhythmia Service, Department of Cardiology, Children's Hospital Boston, Boston, MA

The types of patients different subspecialists jointly manage often provide insights regarding shared pathophysiology and common treatment strategies. During the past decade, as cardiologists have increasingly recognized the subset of adolescents with multiple somatic symptoms and marked orthostatic tachycardia, our

Address correspondence and reprint requests to Mark E. Alexander, MD, Dept of Cardiology, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115 (e-mail: mark.alexander@cardio.chboston.org).

The author reports no conflicts of interest.

gastroenterology colleagues have started recognizing similar symptom complexes in teens with functional gastrointestinal disorders.

PATHOPHYSIOLOGY OF POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

The orthostatic shift, from supine to upright, represents an elegant homeostatic system. With standing there is prompt venous pooling of several units of blood. A feedforward circuit senses this using baroreceptors and via the nucleus tractus solitaris modulates both parasympathetic withdrawal and sympathetic activation. Together these changes result in peripheral vasoconstriction, increased cardiac inotropy, and a modest increase in heart rate that rapidly damps to near-baseline levels. Experimental data from a variety of sources have demonstrated that the homeostatic system is best viewed as a complex engineering system that has multiple sensors, amplifiers, and interactions. Each of these has a gain (slope of response) and a time constant (delay in response). Like any such engineering system the response oscillates, typically within a stable operating range.

Syncope, or fainting, represents a failure of this operating system (1,2). A reasonable analogy is a stereo with the volume higher than the system can handle. After a period of distortion, the circuit breakers turn off to protect the overall system. With syncope there are 2 classically recognized patterns, the cardioinhibitory pattern most apparent in the pauses seen in needle phobia and a vasodepressor pattern characterized by acute loss of peripheral resistance. Not surprising, most common faints are a combination of these 2 normal, although exaggerated, physiological responses.

These episodes of neurally mediated syncope are common. At least 20% of adults report having fainted. The incidence appears to peak in the teen years, with a marked female predominance. There is a typical prodrome, which correlates with exaggerated swings in heart rate and blood pressure. During this period, which can last minutes, patients report lightheadness, warmth, weakness, and more than half report nausea. They become pale and collapse; while they regain consciousness quickly, they have residual symptoms of fatigue, headache, and often other symptoms for minutes. There are often obvious triggers of prolonged standing, acute illness, and stress. This syndrome is well recognized by clinicians.

POTS is a variant of neurally mediated syncope recognized by a marked (30–40 bpm) increase in heart rate either during a formal head-up tilt test (HUTT) or during 3- to 10-min stand tests in the office. Originally described in young adult women by Low and colleagues at the Mayo Clinic, the clinical syndrome is characterized by multiple somatic symptoms, similar to the prodrome and residual symptoms of a common faint. Like syncope patients, nearly 50% of patients have significant gastrointestinal symptoms (3,4). A majority of these patients do not faint, probably because of a combination of their compensatory tachycardia and because they have learned sufficient additional adaptive techniques. Although the precise pathophysiology of POTS remains obscure, there are a number of insights that inform our current understanding. Julian Stewart, a cardiologist at New York Medical College, has done the most systematic evaluation of adolescents with POTS. The critical observations have been excessive venous pooling not just in the legs but also in the pelvic and splanchnic venous compartments, with marked decrease in the thoracic blood pool (5). Despite the brisk heart rate increase, which succeeds in maintaining mean arterial blood pressure, there are at least transient declines in cerebral blood flow velocity, in part mediated by hypocapnea and relative hyperventilation. The majority of the data suggest that despite this shift in cerebral blood flow velocity and cerebral oxygenation, cerebral autoregulation remains intact. Similarly, despite the exaggerated sympathetic activation, most measures of baroreflex integrity are normal. There are variable neuroendocrine correlates. Many have decreased blood volume, although paradoxically they have normal plasma renin and low serum aldosterone (6). In addition, there is at least a subset of patients with increased angiotensin II and decreased cutaneous nitric oxide suggesting endothelial dysfunction (7,8). This pattern is different either from the acute but self-correcting heart rate increase seen in many adolescents and adults immediately upon standing, and from the steady loss of blood pressure seen in acute volume depletion or in adults with neurally mediated hypotension.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

POTS, by definition, implies that the orthostatic tachycardia is an idiopathic disorder neither associated with a systemic autonomic neuropathy nor with a global medical condition. There are a number of systemic disorders that include significant orthostasis (Table 1). Malnutrition and anorexia nervosa probably represent the most relevant part of this differential diagnosis in teenagers. Rapid weight loss, even while maintaining a reasonable body weight, can exacerbate symptoms. In contrast to many of the primary autonomic disorders, baseline baroreflex function is normal in patients with POTS. Although a brief screen for systemic disease is warranted, a general physical examination, hemogram, and serum chemistries and probably thyroid screen give a relatively comprehensive initial screen. Despite some incidence of low-grade palpitations (typically hard and

TABLE 1. *Diseases with high frequency of autonomic symptoms*

Primary	Secondary	Uncertain/"Functional"
Hereditary and sensory neuropathies familial dysautonomia	Mitochondrial disease	Postural tachycardia
CIPA/congenital pain insensensivity (IV)	Malnutrition/anorexia	Syncope
Allgrove (3 or 4 A) syndrome	Endocrine: Adrenal Thyroid Diabetic (rare)	Chronic fatigue (some)
Central hypoventilation/Ondine's curse	Acute illness/fever	Chronic abdominal pain/IBS
Dopamine β-hydroxylase deficiency	Chemotherapy	Complex regional pain syndrome (reflex sympathetic dystrophy)
Spinal cord injury	Drugs	Raynaud
Neurodengerative/encephalopathy		

not rapid heart beats), there is remarkably little overlap with true cardiovascular disease or arrhythmias.

RECOGNIZING AND DIAGNOSING POTS

The diagnosis of POTS is relatively straightforward and does not preclude other diagnoses. At its most basic, POTS is the observation that there is an exaggerated orthostatic heart rate increase, typically 30 bpm during orthostatic vital signs, and 30 to 40 bpm or heart rate >120 bpm 6 min into a 60° to 70° HUTT. For an adolescent, changes of <30 bpm during either of these evaluations are likely physiological. In addition, there should be some presence of typical orthostatic symptoms, although teens may have a difficult time articulating precise symptoms. Screening patients with a brief review of symptoms and formal orthostatic vital signs (supine heart rate and blood pressure that is repeated at 3 minutes; heart rate and blood pressure 1 and 3 minutes after standing) can be done relatively quickly in a busy office environment (Table 2).

Further diagnostic testing (Table 3) is probably not required to consider the diagnosis and initiate therapy. In the author's practice, testing is largely reserved for patients (or physicians) refractory to initial therapy. HUTT deserves specific attention. Conceptually simple, patients are outfitted with monitoring that includes at least continuous heart rate and intermittent blood pressure. Additional monitoring used in specialized laboratories can include impedence cardiography, cerebral artery Doppler, venous capacitance, end tidal CO_2 and more continuous arterial pressure monitoring. Once instrumented, patients are tilted up to 60° to 70° and observed for 6 to 30 minutes. Patients often find the test intolerable. Prolonged (longer than 16 minutes) and steep (>70°) tilts may have up to a 40% incidence of physiologically positive faints in adolescents (9,10). It can be particularly challenging to identify nonoverlapping patterns with even more complicated autonomic testing in adolescents, in part because they have a developmentally maximal amount of sinus arrhythmia and high levels of physiological orthostasis. Using an extensive battery of provocative HUTT testing and subsequent analysis, the author and colleagues evaluated patients with complex regional pain syndrome, who have a high frequency of autonomic symptoms and signs, and the only reliable difference between controls and between pre- and posttherapy visits was the presence of orthostatic tachycardia (11).

Most tests have been tried in systematic evaluations in which, despite limitations, they can provide useful physiological insights. In this setting shallow tilt angles can distinguish patients with chronic fatigue from age-matched controls (12). More comprehensive autonomic testing batteries can identify abnormalities missed in rapid clinical screens (13,14). Referral and ascertainment bias further complicate interpretation of data regarding links between orthostasis and other complaints. Although adolescents with sufficient disability to be labeled as having chronic fatigue syndrome do have a high incidence of orthostatic findings (both by tilt and examination), comparison of cohorts of adults with chronic fatigue to

TABLE 2. *Rapid clinical screen for orthostatic disorders*

Symptom review	
Overall well-being	10-point visual analogue scale (10 = well)
Dizziness and lightheadness	10-point visual analogue scale (10 = severe)
	Subjective symptoms
Syncope	Frequency
Peripheral vascular phenomenon	Livedo, Raynaud
Palpitations	Describe
School attendance	
Exacerbating Features	Standing
	Exercise
	Daytime variation
	Menstrual/abdominal cramps
Physical examination	
Supine cardiac examination	Normal
Orthostatic heart rate and blood pressures	0, 3 min supine, 1, 3 min standing

TABLE 3. *Diagnostic testing for postural tachycardia and autonomic function in the patient with POTS*

	Ease	Cost	Level of evidence
Orthostatic vital signs	++++	¢	I
Holter, heart rate variability	+++	$$$	IIb
Head-up tilt (classic)	+ or −	$$$ or ¢	IIb
Sympathetic nerve traffic	−	Research	I for specific questions, IIb or III for most
Provocative heart rate variability	−	Research	Research
Regional venous capacitance	−	Research	Research
Sudomotor axon test	++	$$	IIa/I for specific question
Enhanced tilts	−	$$$ or research	Research, IIb
Thermoregulatory evaluation	−	Research	Research

Relative cost indicated as ¢-$$$$ and relative level of evidence using standard class I, IIa, IIb and III classifications.

controls has not suggested a high incidence of orthostatic findings. Chronic pain, decreased activity, malnutrition, medications, and psychological concerns may increase either the symptoms profile or exacerbate some of the physiology.

THERAPY OPTIONS FOR POTS

Because the primary findings, heart rate and blood pressure, are readily measurable, the cardiovascular autonomic responses can be targeted for therapy. The natural history of POTS includes a relatively high frequency of spontaneous recovery for 2 to 3 years, which complicates judging any therapy. The foundation of therapy (Table 4) starts with nonpharmacological approaches that overlap with therapies for many chronic pain syndromes. This approach includes doing regular weight-bearing exercise, getting adequate sleep and hydration, considering the wearing of compression stockings to decrease peripheral venous pooling, and coaching patients on active anti-gravity maneuvers to augment blood pressure during postural change. Subsequent drug therapy is imperfect. The mineralocorticoid fludrocortisone, intended to increase blood volume, is the historical choice. Although a generally accepted therapy, there are no double-blind placebo-controlled trials supporting its use. Direct pressor agents, primarily midodrine hydrochloride, can rapidly increase afterload and decrease symptoms in well-designed studies. They require frequent dosing and an engaged patient. Well-designed but small studies have effectively used the peripheral muscarinic blocker pyridostigmine to enhance parasympathetic effects. Serotonin reuptake inhibitors have anecdotal data supporting their use, even in the absence of concomitant depression (15,16). Beta-blockers, although popular, have failed most controlled trials. Anecdotal data for other agents have not been systemically studied or embraced. Although not evaluated specifically for POTS, cognitive behavioral therapy is an accepted part of managing refractory syncope and patients disabled by chronic fatigue. Low doses of tricyclic antidepressants such as amitriptyline used for chronic pain do not seem to have significant cardiac side effects in most people.

CONCLUSIONS

POTS is a relatively chronic, idiopathic disorder of adolescents and young adults that may include abdominal symptoms. A rapid office screen of orthostatic vital signs and focused review of symptoms is likely to accurately identify at least a subgroup of recurrent abdominal pain patients who also have POTS features. Accurately

TABLE 4. *Therapy choices for syncope and postural tachycardia*

	Ease	Cost	Level of evidence
Nonpharmacological	++++	¢	I
Midodrine	+	$$	I/IIa (+DBPC for POTS)
Fludrocortisone	++	$	II (consensus, limited DBPC)
β-Blocker	++	¢	IIb (fails DBPC)
Clonidine (low dose)	+	$	IIb (anecdote)
Pyridostigmine	+	$	IIa (+DBPC, limited)
Serotonin reuptake inhibitors	+	$$	IIb (anecdote)
Erythopoeitin	−	$$$	IIb (anecdote)
Pacemakers	−	$$$$	II (mixed)

POTS, postural orthostatic tachycardia syndrome; DBPC, double-blind placebo-controlled data. Relative cost indicated as ¢-$$$$ and relative level of evidence using standard class I, IIa, IIb and III classification.

characterizing what role POTS plays in these patients will likely require a series of systematic investigations, both with simple and more complicated physiological probes, and with controlled therapeutic approaches. There are not yet sufficient data to understand how much overlap there is between the cohorts of patients with recurrent abdominal pain and those with POTS (17).

REFERENCES

1. Saul JP, Alexander ME. Reflex and mechanical aspects of cardiovascular development: techniques for assessment and implications. *J Electrocardiol* 1998;30:57–63.
2. DiVasta AD, Alexander ME, DiVasta AD, et al. Fainting freshmen and sinking sophomores: cardiovascular issues of the adolescent. *Curr Opin Pediatr* 2004;16:350–6.
3. Sandroni P, Opfer-Gehrking TL, McPhee BR, et al. Postural tachycardia syndrome: clinical features and follow-up study. *Mayo Clin Proc* 1999;74:1106–10.
4. Sullivan SD, Hanauer J, Rowe PC, et al. Gastrointestinal symptoms associated with orthostatic intolerance. *J Pediatr Gastroenterol Nutr* 2005;40:425–8.
5. Stewart JM, Medow MS, Glover JL, et al. Persistent splanchnic hyperemia during upright tilt in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2006;290:H665–73.
6. Raj SR, Biaggioni I, Yamhure PC, et al. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation* 2005;111:1574–82.
7. Stewart JM, Taneja I, Glover JL, et al. Angiotensin II type 1 receptor blockade corrects cutaneous nitric oxide deficit in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2007;292:H1420–6.
8. Stewart JM, Medow MS, Minson CT, et al. Cutaneous neuronal nitric oxide is specifically decreased in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2007;293:H2161–7.
9. Lewis DA, Zlotocha J, Henke L, et al. Specificity of head-up tilt testing in adolescents: effect of various degrees of tilt challenge in normal control subjects. *J Am Coll Cardiol* 1997;30: 1057–60.
10. de Jong-de Vos van Steenwijk CC, Wieling W, Harms MP, et al. Variability of near-fainting responses in healthy 6–16-year-old subjects. *Clin Sci (Colch)* 1997;93:205–11.
11. Meier PM, Alexander ME, Sethna NF, et al. Complex regional pain syndromes in children and adolescents: regional and systemic signs and symptoms and hemodynamic response to tilt table testing. *Clin J Pain* 2006;22:399–406.
12. Wyller VB, Due R, Saul JP, et al. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. *Am J Cardiol* 2007;99:997–1001.
13. Lambrecht R, McNeeley K, Tusing L, et al. Evaluation of a brief cardiovascular autonomic screen. *Auton Neurosci* 2007;131:102–6.
14. Chelimsky G, Boyle JT, Tusing L, et al. Autonomic abnormalities in children with functional abdominal pain: coincidence or etiology? *J Pediatr Gastroenterol Nutr* 2001;33:47–53.
15. Lahrmann H, Cortelli P, Hilz M, et al. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurol* 2006;13:930–6.
16. Medow MS, Stewart JM, Sanyal S, et al. Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol Rev* 2008;16:4–20.
17. Hyman PE, Danda CE. Orthostatic intolerance and the biopsychosocial model. *J Pediatr Gastroenterol Nutr* 2005;40: 423–4.

Will the Rome Criteria Help Pediatrics?

Paul E. Hyman

Professor of Pediatrics, Louisiana State University Health Sciences Center, New Orleans

The Rome Foundation mission statement sets goals designed to ''improve the lives of people with functional gastrointestinal disorders (FGIDs).'' Those goals are to ''promote clinical recognition and legitimization of FGIDs, and develop a scientific understanding of their pathophysiological mechanisms and achieve optimal treatment'' (1). The purpose of this article is to review progress toward achieving those goals in pediatrics, and to suggest means to further successes.

In 1997 seven pediatric gastroenterologists met together in Rome to create the first set of symptom-based criteria for diagnosis of pediatric functional gastrointestinal disorders, named the Rome II criteria (2). Seven years later 2 working teams revised the pediatric FGIDs. These working teams improved the initial criteria based on research published during the preceding years (3,4). The criteria will continue to be revised as more is learned about them. So far, the criteria have had more impact on research than on clinical care. Pediatric psychologists and gastroenterologists were quick to assess the validity

Address correspondence and reprint requests to Paul E. Hyman, MD, Children's Hospital, Division of Gastroenterology, 200 Henry Clay Ave, New Orleans, LA 70118

The author reports no conflicts of interest.

of the criteria (5–9) and to suggest improvements. For example, only 60% of children with functional constipation met Rome II criteria for functional fecal retention (10,11). These data prompted a European consensus conference to suggest new, more inclusive criteria (12). The European critique was constructive, so that the outcome was one of satisfaction and inclusion rather than splitting. In Rome III there was a name change to functional constipation, and the criteria were expanded and modified in an attempt to include more of the population. In addition to validation studies, the criteria have stimulated research in the epidemiology (5,6,13), pathophysiology, and treatment trials for FGIDs. In exploring the pathophysiology of abdominal pain, barostat studies of pressure and volume relations with symptoms have shown patterns similar to those already described in adults, with irritable bowel syndrome being associated with colon hyperalgesia and dyspepsia with gastric hyperalgesia (14–16). To avoid the discomfort of inflating a balloon in a hollow viscus, some pediatric investigators are experimenting with nutrient meals (17) or a water load test (18). Treatment trials are under way, with attention to drugs: either old, such as amitriptyline (19) or new, such as citralopam (20). As they do in adults, cognitive behavioral therapy (21) and hypnosis (22) appear to work for children with stomachaches.

Other functional disorders are sought for nomination to the list of pediatric FGIDs. Rome II publications recognized infant dyschezia as an entity with characteristics distinct from those of functional constipation. In Rome III, infant colic and adolescent rumination syndrome were added to the list of FGIDs. There were insufficient data for accepting childhood biliary dyskinesia (23) as a functional disorder. Other conditions may be awaiting a careful descriptive study: infants who do their best sucking during twilight sleep but nipple fitfully and reluctantly while awake, or preteens and teens who awaken before dawn because of nausea and vomiting or abdominal pain and diarrhea that resolves by late morning. The Rome Working Team stated that disorders involving abdominal pain will be limited to children who can provide an accurate pain history. The team's decision excluded nonverbal infants and toddlers as well as some autistic and children with cognitive delays from having irritable bowel syndrome or functional dyspepsia. Practical solutions need to be found to include nonverbal children in future revisions of the criteria.

A large majority of childhood headaches, stomachaches, and other somatic aches and pains are not from disease. Chronic defecation disorders, abdominal pain, and repeated daily infant regurgitation account for a majority of pediatric gastroenterology clinic visits. There are no tests for FGIDs, but diagnoses can be made from the history, when the history fits symptom-based (Rome) criteria and there are no symptoms or physical signs of disease. Despite an increase in published research, and multiple collaborations among clinical investigators, the front lines of medical care have not heard of Rome criteria. In data presented at this meeting, Schurman and colleagues surveyed North American Society of Gastroenterology, Hepatology, and Nutrition (NASPGHAN) members. A majority of pediatric gastroenterologists knew that Rome criteria existed, but only a handful used them in practice (24). The Rome criteria have the potential to improve pediatric health care and save millions of dollars. Increased comfort of primary care clinicians in diagnosing and treating infant regurgitation, functional constipation, and childhood stomachaches would save worries and costs of medical workups, inappropriate management, and inadvertent co-creation of disease. No tests are necessary or desirable when there is a functional diagnosis because all tests come back negative. When tests are done, each negative test worries parents that something is being missed. For example, half of all healthy infants regurgitate 2 or more times each day (25). Half of the mothers of these infants perceive this symptom as a problem. In the United States alone, that means there are more than 1 million anxious mothers every year, requesting help from their primary care clinician. Yet the infants have a transient, harmless symptom that is within the normal range of behaviors for age. What if there were pamphlets in the waiting area about infant regurgitation, a placard on the wall explaining the diagnosis, and a clinician who could answer the 4 questions asked by every parent: What is wrong? Is it dangerous? Will it go away? What can we do? It's infant regurgitation. It's not dangerous. It goes away by the end of the first year. You are not obligated to do anything, but you can consider using thickened formula, upright postures after eating, and avoid overfeeding. The same approach will work for the other 2 most common conditions referred to pediatric gastroenterologists: functional constipation and functional abdominal pain. Recovery from functional constipation is correlated with the duration of symptoms (26). Stomachaches affect about 1 in 5 children and adolescents. Nearly all childhood stomachaches are functional, and about 80% of histories from children with chronic or recurrent abdominal pain met symptom-based criteria for 1 or more FGIDs (5). Opportunities for early diagnosis and effective treatment are with primary care clinicians.

What must happen for Rome criteria to become part of the primary care lexicon? An example for changing pediatric primary care behavior exists in our recent pedi-gastro history. Gastroesophageal reflux disease (GERD) gained the interest of pediatric gastroenterologists when the technology to measure it arrived. Fiberoptic endoscopy and pH metry expanded pediatric gastroenterologist interest in GERD in the 1980s; however, primary care clinicians were not tuned in to infant gastroesophageal reflux until pharmaceutical companies took notice of the pediatric marketplace. In the

mid-1990s the American Pseudo-obstruction and Hirschsprung's Disease Society, a parent support group, accepted a grant from Janssen Pharmaceutica to develop the Pediatric Community Outreach Program. The program's medical advisory board developed a slide kit and other materials to teach primary care clinicians about GERD. Pediatric gastroenterologists agreed to lecture to primary care clinicians. A new series of lectures were later supported by pharmaceutical companies marketing proton pump inhibitors (PPIs). Those talks were the second wave of information for the primary care clinician. Finally, NASPGHAN and Children's Digestive Health and Nutrition Foundation developed another GERD slide kit and speakers' bureau. There was a third wave of information for the primary care clinician. Three waves of physician-to-physician communication during the past decade, plus advertising in journals, radio, and television seem to have parents asking about and primary care clinicians treating GERD before they refer to the subspecialist.

During the past 20 years the pendulum may have swung too far, as thousands of healthy infants with infant regurgitation are first treated with PPIs, and then referred to gastroenterologists because the PPI did not alter the regurgitation. This example of changing thinking and prescribing habits provides a framework for how to impress the importance of the FGIDs and Rome criteria upon the pediatrician.

Expect that it will take a decade to direct clinicians and families away from a disease-oriented model and toward understanding pediatric FGIDs. We anticipate the need for 3 waves of community teaching to help primary care clinicians adapt to the shift in thinking and behavior. A committed core group will instruct pediatric gastroenterologists about the FGIDs and demonstrate to them how using Rome criteria will be good for children and good for their professional practices. Indeed, the contemporary pediatric gastroenterologist already takes time each day to evaluate and treat healthy children with an FGID, anxious parents, and an anxious referring clinician. The anxiety accrues from diagnostic uncertainties. If primary care clinicians identified and treated FGIDs at the first visit, then families would feel better, clinicians would feel more competent, and subspecialists would feel free to care for unusual patients requiring the attention and commitment of a subspecialist.

I believe that the pediatric gastroenterology community will take the lead in teaching about FGIDs to primary care clinicians. A 10-year plan for change that includes speakers' bureaus, wall placards, educational pamphlets, and so forth may cost about $10 million. Implementation of such a plan may save that much in health care costs in the first year. Where will the funding come from? The Rome Foundation has promised a beginning. Perhaps other advocacy organizations such as the International Foundation for Functional Gastrointestinal Disorders, American Academy of Pediatrics, or NASPGHAN will contribute. Regardless of where the funding comes from, pediatric gastroenterologists will have recognized the importance of FGIDs to child health.

REFERENCES

1. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA (ed). *Rome III: The Functional Gastrointestinal Disorders.* McLean, VA: Degnon Associates; 2006. pp. p. 16.
2. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut* 1999;45 (Suppl II): II60–II68.
3. Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
4. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders:child/adolescent. *Gastroenterology* 2006;130:1527–37.
5. Walker LS, Lipani TA, Greene JW, et al. Recurrent abdominal pain: symptom subtypes based on the Rome II criteria for pediatric functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2004;38:187–91.
6. Caplan A, Walker L, Rasquin A. Validation of the pediatric Rome II criteria for functional gastrointestinal disorders using the questionnaire on pediatric gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 2005;41:305–16.
7. Caplan A, Walker L, Rasquin A. Development and preliminary validation of the questionnaire on pediatric gastrointestinal symptoms to assess functional gastrointestinal disorders in children and adolescents. *J Pediatr Gastroenterology Nutr* 2005;41:296–304.
8. Schurman JV, Frisen CA, Danda CE, et al. Diagnosing functional abdominal pain with the Rome II criteria: parent, child, and clinician agreement. *J Pediatr Gastroenterol Nutr* 2005;41: 291–5.
9. Saps M, Di Lorenzo C. Interobserver and intraobserver reliability of the Rome II criteria in children. *Am J Gastroenterol* 2005;100: 2079–82.
10. Voskuijl WP, Heijmans J, Heijmans HS, et al. Use of Rome II criteria in childhood defecation disorders: applicability in clinical and research practice. *J Pediatr* 2004;145:213–7.
11. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. *J Pediatr* 2005;146:359–63.
12. Benninga M, Candy DC, Catto-Smith AG, et al. The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. *J Pediatr Gastroenterol Nutr* 2005;40:273–5.
13. Chial HJ, Camilleri M, Williams DE, et al. Rumination syndrome in children and adolescents: diagnosis, treatment, and prognosis. *Pediatrics* 2003;111:158–62.
14. Van Ginkel R, Voskuijl WP, Benninga MA, et al. Alterations in rectal sensitivity and motility in childhood irritable bowel syndrome. *Gastroenterology* 2001;120:31–8.
15. Di Lorenzo C, Youssef NN, Sigurdson L, et al. Visceral hyperalgesia in children with abdominal pain. *J Pediatr* 2001;139:838–43.
16. Faure C, Wieckowska A. Somatic referral of visceral sensations and rectal sensory threshold for pain in children with functional gastrointestinal disorders. *J Pediatr* 2007;150: 66–71.
17. Chitkara DK, Delgado-Aros S, Bredenoord AJ, et al. Functional dyspepsia, upper gastrointestinal symptoms, and transit in children. *J Pediatr* 2003;143:609–13.
18. Walker LS, Williams SE, Smith CA, et al. Parent attention versus distraction; impact on symptom complaints by children with and without chronic functional abdominal pain. *Pain* 2006;122: 43–52.
19. Bahar RJ, Collins BS, Steinmetz B, et al. Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents. *J Pediatr* 2008;152:685–9.

20. Campo JV, Perel J, Lucas A, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 2004;43:1234–42.
21. Youssef NN, Rosh JR, Loughran M, et al. Treatment of functional abdominal pain in childhood with cognitive behavioral strategies. *J Pediatr Gastroenterol Nutr* 2004;39:192–6.
22. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SC, et al. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: a randomized controlled trial. *Gastroenterology* 2007;133:1430–6.
23. Dumont RC, Caniano DA. Hypokinetic gallbladder disease: a cause of chronic abdominal pain in children and adolescents. *J Pediatr Surg* 1999;34:858–61.
24. Schurman JV, Hunter HL, Friesen CA. Conceptualization and treatment of functional gastrointestinal disorders in pediatric gastroenterology practice. Abstract presented at NASPGHAN Annual Scientific Meeting, October 25–27, 2007.
25. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastro esophageal reflux during infancy. *Arch Pediatr Adolesc Med* 1997;15:569–72.
26. Loening-Baucke V. Functional fecal retention with encopresis in childhood. *J Pediatr Gastroenterol Nutr* 2004;38:79–84.

Pharmacology

Alyssa A. LeBel

Senior Associate in Pain Medicine and Neurology, Department of Anesthesiology and Neurology, Children's Hospital Boston, Boston, MA

Pharmacological interventions for functional gastrointestinal disorders (FGIDs) are based on an evolving understanding of bidirectional brain–gut interactions, the ''brain-gut axis.'' Functional abdominal pain (FAP) and irritable bowel syndrome (IBS) are considered states of dysregulation within the enteric and the central nervous systems, resulting in alterations in sensation, motility, and possibly, immune system function. Brain–gut interactions may tonically or phasically up- or downregulate visceral afferent sensitivity, homeostatic reflexes, and ultimately conscious pain perception (1,2). Therefore, the targets of pharmacotherapy are within the entire pain transmission system, from the peripheral receptors in the gut responding to distension and chemical, osmotic, and thermal stimulation, through the dorsal horn and interneurons of the spinal cord, and ultimately to the levels of conscious perception in the cortex. By definition, visceral sensation is both sensory discriminative and affective motivational. Therefore, visceral pain may be attenuated by neuropathic pain medications, including agents used for nerve pain and mood disorders, as well as novel compounds in development. Such medications include sedatives and anxiolytics, antidepressants, serotonin and 5HT-3 receptor antagonists, somatostatin receptor agonists, and antiseizure agents.

As for most pediatric treatment modalities, published controlled trials are rare. There are 3 reported studies in children with FAP for peripheral, non-neuropathic agents and 1 study for behavioral therapy. Evidence of efficacy is documented to be greater than placebo for famotidine for functional dyspepsia, pizotifen for abdominal migraine, peppermint oil for IBS, and behavioral interventions for FAP (3–6).

Abdominal pain is associated with visceral hypersensitivity and abnormal perception of visceral sensations. Control subjects and patients with functional dyspepsia localize rectal pain during barostat examination to the S3 dermatome, but patients with FAP and IBS localize pain to aberrant dermatomal sites and have a decreased rectal sensory threshold (7). Such findings in children are similar to adult studies of visceral sensitivity in patients with FGIDs (8).

Although the majority of research in the treatment of FGIDs in children has focused on the overall success of cognitive-behavioral therapies, there is an evolving literature regarding the use of pharmacology for receptors along the brain–gut axis. A brief review of some current studies follows.

SEDATIVES AND ANXIOLYTICS

In patients with abdominal pain and comorbid psychological symptoms, these agents are a logical choice

Address correspondence and reprint requests to Alyssa A. LeBel, MD, Pain Management Service, Children's Hospital Boston, 333 Longwood Ave, 5th Floor, Boston, MA 02115 (e-mail: Alyssa.lebel@childrens.harvard.edu).

The author reports no conflicts of interest.

because they modulate overlapping central nervous system circuits involved in emotion, autonomic stress responses, and pain. There is no significant evidence per clinical trials that these agents are effective, and there are numerous clinical reports of limiting adverse effects, such as sedation and addiction, especially prominent in chronic conditions (8). As an example, buspirone, a 5HT1A agonist and anxiolytic drug, effects colonic motility and stress responses in an animal model, decreases dyspepsia in some functional dyspepsia patients, but has no effect on bowel and sensory symptoms in human control subjects (9–11).

ANTIDEPRESSANTS

Of all of the medications available for the treatment of FAP, these agents have been studied the longest (12) and are most familiar to clinicians. They have both central and peripheral nervous system actions appropriate for patients with FGIDs, such as anticholinergic effects, gastrointestinal transit slowing, fundic relaxation, sleep restoration, potential treatment of comorbid depression, and analgesia due to receptor binding throughout the pain transmission system. In addition, there is a detailed literature of their use in multiple chronic pain disorders, including nerve-injury pain, fibromyalgia, and headache (12,13).

Tricyclic antidepressants (secondary and tertiary amines), serotonin reuptake inhibitors (SSRIs; eg, citalopram), and monoamine uptake inhibitors (eg, duloxitene, velafaxine), show improvement of functional GI symptoms in patients with FGIDs in published reports. However, the design and analysis of the studies are variable. In 1 adult randomized placebo-controlled trial of patients with IBS without comorbid depression, subjects treated with an SSRI reported significant decreased abdominal pain and bloating and increased overall well-being (14). In an open-label 12-week flexible dose pediatric study (subjects 7–18 years old), 84% of patients with FAP reported improved function with decreased pain, depression, anxiety, and other somatic complaints (15). Newer monoamine uptake inhibitors affect descending serotonergic and adrenergic pain inhibition systems and show some evidence of analgesia in patients with fibromyalgia and diabetic neuropathy (16,17). Amitriptyline is best studied in pediatric patients with migraine but without placebo-controlled evidence. Open-label studies support efficacy greater than propranolol and cyproheptadine in 50% to 60% of children (18). In 1 pediatric study, 80% of children showed a >50% improvement in symptoms with titration of drug of 0.25 to $1\,mg \cdot kg^{-1} \cdot day^{-1}$ over 8 to 10 weeks (19). Nortriptyline is reported in some studies to have an increased risk for cardiac arrhythmias. SSRIs have not been adequately studied in the pediatric population. With prescribing these agents to children and adolescents, it is recommended to provide appropriate information regarding depression and suicidal ideation for patients and families. A Web site with data updated by the American Pediatric Association and American Academy of Child and Adolescent Psychiatry is *ParentsMedGuide.org*. The site notes "The FDA [Food and Drug Administration] reported an increase in spontaneous reports of suicidal thoughts and/or behavior among children receiving medication, but there is no evidence that these suicidal thoughts or behaviors lead to an increased risk of suicide" (20).

ANTISEIZURE MEDICATIONS

Although there are no specific trials involving antiseizure agents for pediatric FGIDs, these medications have been increasingly used, off-label, for neuropathic pain conditions, such as migraine and neuralgia, in children. There is a significant adult literature for their efficacy in diabetic neuralgia, postherpetic neuralgia, and migraines and safety and efficacy data for their use in pediatric seizure disorders. Generically, they depress abnormal neuronal discharges and raise the inappropriately lowered threshold of sensitized neurons, such as those also present in states of visceral hyperalgesia. Much of the pediatric experience is with these agents for seizure management. Their use as analgesics is extrapolated from adult experience. The first-generation agents, such as phenytoin and carbamazepine, are associated with serious adverse effects and require regular blood level monitoring. The second-generation medications, such as gabapentin, lamotrigine, topiramate, zonisamide, levetiracetam, and pregabalin, may not require laboratory monitoring, have fewer sedation or cognitive effects, and less overall adverse effects. Caution is advised with their use because the pediatric experience with these agents is limited and the true incidence of serious side effect profile is not fully known.

SEROTONIN AND 5HT-3 RECEPTOR ANTAGONISTS

Serotonin (5HT) receptors are attractive candidates for pharmacotherapy in FGIDs because greater than 80% of serotonin is stored in the enterochromaffin cells of the gut. With mechanical or chemical stimulation or experimental stress, serotonin acts in a paracrine fashion on its receptors on intrinsic and afferent (vagal and spinal) nerve terminals. Two 5HT-3 compounds studied in adults, alosteron and cilansteron, have shown efficacy in patients with diarrhea-predominant IBS, but complications of severe constipation, ischemic colitis, and perforations have prompted FDA restrictions. A 5HT-4 antagonist, tegaserod, is in limited use (21–23).

SOMATOSTATIN RECEPTOR AGONISTS (SSTS)

Somatostatin receptor agonists (SSTs) have been available for the past 30 years as antisecretory agents. Recently, broader use has been considered because SST receptors are localized in both the GI tract and the central nervous system, with SST2 receptors located on spinal afferents, superficial dorsal horn spinal neurons, and within the locus ceruleus. Octreotide, a nonselective SST2, SST3, and SST5 receptor agonist, has analgesic efficacy in FGIDs, but has limited clinical use due to its parenteral formulation, inhibition of gallbladder emptying, and receptor desensitization with chronic use (24).

CANDIDATE MEDICATIONS IN DEVELOPMENT

Neurokinin (NK) receptor antagonists, potentially binding to NK1R (SP), NK2R (NKA), and NK3R (NKB) within the autonomic, enteric, and central nervous systems, have effect on intestinal motility, secretion, and visceral sensitivity in states of chronic pain and central sensitization. Corticotropin-releasing factor (CRF) receptor antagonists which bind to CRF 1 and 2 receptors have been shown to modulate the effect of stress on GI function. Other potential modulators of peripheral and central visceral hyperalgesia include α-adrenergic agonists (clonidine), cholecystokinin antagonists, *N*-methyl-D-aspartic acidantagonists (ketamine), and transient receptor potential ion channel antagonist of the vanilloid type.

REFERENCES

1. Craig AD. How do you feel? Interoception: the sense of the physiologic condition of the body. *Nat Rev Neurosci* 2002;3: 655–66.
2. Porreca F, Ossipov MH, Gebhart GF. Chronic pain and medullary descending facilitation. *Trends Neurosci* 2002; 25: 319–25.
3. Weydert JA. Systematic review of treatments for recurrent abdominal pain. *Pediatrics* 2003;111:e1–1.
4. Huertas-Ceballos A, McArthur C, Logan S, Pharmacologic interventions for recurrent abdominal pain. *Cochrane Database Syst Rev* 2002; CD003017.
5. See MC, Birnbaum AH, Schecter CB, et al. Double-blind, placebo-controlled trial of famotidine in children wit abdominal pain and dyspepsia. *Dig Dis Sci* 2001;46:985–92.
6. Symon DN, Russell G. Double-blind placebo-controlled trial of pizotifen syrup in the treatment of abdominal migraines. *Arch Dis Child* 1995;72:48–50.
7. Faure C. Somatic referral of visceral sensations and rectal sensory threshold for pain in children with functional gastrointestinal disorders. *J Pediatr* 2007;150:66–71.
8. Mayer EA, Tillisch K, Bradesi S. Modulation of the brain-gut axis as a therapeutic approach in gastrointestinal disease. *Aliment Pharmacol Ther* 2006;24:919–33.
9. Martinez JA, Bueno L. Buspirone inhibits corticotrophin-releasing factor and stress-induced cecal motor response in ratsby acting through 5-HT1A receptors. *Eur J Pharmacol* 1991;202: 379–83.
10. Tack J, Piessevaux H, Coulie B, et al. A placebo-controled trial of buspirone, a fundus-relaxing drug, in functional dyspepsia: effect on symptoms and gastric sensory and motor function. *Gastroenterology* 1991;116:A325.
11. Chial HJ, Camilleri M, Ferber I, et al. Effects of venlafaxine, buspirone, and placebo on colonic snsorimotor functions in healthy humans. *Clin Gastroenterol Hepatol* 2003;1:211–8.
12. Olden KW. The use of antidepressants in functional gastrointestinal disorders: new uses for old drugs. *CNS Spectr* 2005;10: 891–7.
13. Jackson JL, O'Malley PG, Tomkins G, et al. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am J Med* 2000;108:65–72.
14. Tack J, Muller-Lissner S, Bytzer P, et al. A randomized controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* 2005;54:1707–13.
15. Campo JV, Perel J, Lucas A, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. *J Child Adoles Psychiatry* 2004;43:1234–42.
16. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 2005;119:5–15.
17. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005;6: 346–56.
18. Levinstein B. A comparative staudy of cyproheptadine, amitriptyline, and propranolol in the treatment of adolescent migraine. *Cephalagia* 1991;11:122–3.
19. Hershey AD, Powers SW, Benitti AL, et al. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000;40:539–49.
20. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicidal attempts in pediatric antidepressant treatment. *JAMA* 2007;297:1683–96.
21. Bradette M, Moennikes H, Carter F, et al. Cilansetron in irritable bowel syndrome with diarrhea predominance: efficacy and safety in a 6 month global study. *Gastroenterology* 2004;126: A-42.
22. Friedel D, Thomas R, Fisher RS. Ischemic colitis during treatment with alosteron. *Gastroenterology* 2001;120:557–60.
23. Talley NJ. 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. *Aliment Pharmacol Ther* 1992;6:273–89.
24. Klooker TK, Beaumont H, Kuilen SD, et al. Octreatide as potential treatment for patients with non-constipated irritable bowel syndrome. *Gastroenterology* 2005;128:A-93–4.

Psychological/Cognitive Behavioral Treatment of Childhood Functional Abdominal Pain and Irritable Bowel Syndrome

Brenda Bursch

Professor of Psychiatry & Biobehavioral Sciences and Pediatrics, David Geffen School of Medicine at University of California, Los Angeles

Outcome studies and meta-analyses reveal that psychological treatments such as hypnotherapy and cognitive-behavioral therapy (CBT) are effective in treating somatic symptoms in adults with functional gastrointestinal (GI) disorders (1,2). Preliminary research suggests that improvements achieved with psychological treatments are similar to (or possibly greater than) those obtained with gut-directed pharmacological treatments. Especially interesting, preliminary research suggests that CBT may have direct effects on GI symptoms, independent of psychological distress (3).

Among children and adolescents with functional abdominal pain or irritable bowel syndrome, initial case studies and retrospective reviews suggested effectiveness of cognitive and behavioral interventions, (4–8) and recent randomized trials (using standard pediatric care as the control group intervention) provide more robust evidence for the effectiveness of psychological treatments (9–14). Cognitive behavioral techniques not only have direct effects on symptoms but also promote self-efficacy by increasing the child's ability to self-manage symptoms. Although parents may need an initial explanation to understand how the techniques can alter physiological function to provide symptom relief, some parents are pleased to avoid medications and their possible side effects. Psychological management strategies include parent training, family interventions, psychotherapy/CBT, relaxation, distraction, hypnotherapy/guided imagery, and biofeedback.

Parent training and family therapy approaches are used to facilitate acceptance of a rehabilitation approach to treatment, alter family patterns that maintain disability or exacerbate symptoms, help parents learn to better tolerate distress, and develop behavioral plans that support the child's self-management of symptoms and independent functioning.

Psychotherapy is used to reduce somatic and psychological symptoms, improve coping and functioning, improve communication and problem solving, and reduce stress load. CBT refers to psychotherapy focused on achieving these goals by modifying unhelpful cognitions, assumptions, beliefs, and behaviors. Techniques may include developing a biopsychosocial view of symptoms; keeping a diary of symptoms and associated events, feelings, thoughts and/or behaviors (to identify triggers and outcomes that could be targeted for intervention); learning relaxation and distraction techniques; questioning cognitions, assumptions, and beliefs that may be unhelpful or unrealistic and trying new ones; and gradually facing activities that may have been avoided.

Relaxation techniques, such as progressive muscle relaxation and controlled breathing, can directly alter pain perception by facilitating a relaxation response (including muscle relaxation, reduced heart rate and blood pressure, and improved mood). Distraction techniques shift attention away from pain and have been shown to increase pain tolerance and decrease pain perception. Distraction techniques vary widely but include formal interventions such as hypnotherapy/guided imagery or everyday distracters like games, television, or school. Some distracters, such as school, can also improve functioning and decrease distress by helping the child gain mastery over difficult situations.

Hypnotherapy and guided imagery can focus attention away from symptoms, alter sensory experiences, reduce distress, induce relaxation, reframe symptom experiences, facilitate dissociation from pain, and enhance feelings of mastery/self-control. These techniques can also be used to solve problems (eg, to imagine being calm during a test) and to feel a sense of accomplishment. ''Gut-directed'' hypnotherapy, which includes gut-specific treatments and suggestions, was developed for individuals with irritable bowel syndrome and digestive disorders. It includes gut-specific treatments and suggestions.

Biofeedback uses a computer paired with controlled breathing, relaxation, or hypnotic techniques. The computer generates a visual or auditory indicator of the child's muscle tension, peripheral skin temperature, or anal control, allowing the child to have external validation of the physiological changes he or she has produced using the techniques.

Address correspondence and reprint requests to Brenda Bursch, PhD, David Geffen School of Medicine at UCLA, Department of Psychiatry and Biobehavioral Sciences, 760 Westwood Plaza, 48-253C NPI, Los Angeles, CA 90024-1759 (e-mail: bbursch@mednet.ucla.edu).

The author reports no conflicts of interest.

Future research on cognitive behavioral treatment of childhood functional GI disorders would benefit from direct comparison of efficacy of psychological compared to medication treatments. If both are found to be equally effective, then research designs may then shift to optimizing combinations of cognitive, behavioral, and medication treatments to maximize effectiveness and patient satisfaction. Research on mechanisms of change will require inclusion of specific and repeated measures of dysfunction, such as anxiety sensitivity, vigilance, pain catastrophizing, self-efficacy, physiological measures, and imaging to test theoretical models. Additional recommendations for future research include the inclusion of comorbid psychopathology, standardized inclusion and exclusion criteria, and standardized outcome measures of childhood pain and functioning.

REFERENCES

1. Whitehead WE. Hypnosis for irritable bowel syndrome: the empirical evidence of therapeutic effects. *Int J Clin Exp Hypn* 2006;54:7–20.
2. Lackner JM, Mesmer C, Morley S, et al. Psychological treatments for irritable bowel syndrome: a systematic review and meta-analysis. *J Consult Clin Psychol* 2004;72:1100–3.
3. Lackner JM, Jaccard J, Krasner SS, et al. How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. *Gastroenterology* 2007;133:433–44.
4. Anbar R. Self-hypnosis for the treatment of functional abdominal pain in childhood. *Clin Pediatr* 2001;40:447–51.
5. Miller AJ, Kratochwill TR. Reduction of frequent stomach complaints by time out. *Behav Ther* 1979;10:211–8.
6. Sank LI, Biglan A. Operant treatment of a case of recurrent abdominal pain in a 10 year old boy. *Behav Ther* 1974;5:677–81.
7. Youssef NN, Rosh JR, Loughran M, et al. Treatment of functional abdominal pain in childhood with cognitive behavioral strategies. *J Pediatr Gastroenterol Nutr* 2004;39:192–6.
8. Duarte MA, Penna FJ, Andrade EM, et al. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. *J Pediatr Gastroenterol Nutr* 2006;43:59–64.
9. Hicks CL, von Baeyer CL, McGrath PJ. Online psychological treatment for pediatric recurrent pain: a randomized evaluation. *J Pediatr Psychol* 2006;31:724–36.
10. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. *J Pediatr Gastroenterol Nutr* 2000;31:47.
11. Robins PM, Smith SM, Glutting JJ, et al. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. *J Pediatr Psychol* 2005;30:397–408.
12. Sanders MR, Shepherd RW, Cleghorn G, et al. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. *J Consult Clin Psychol* 1994;62:306–14.
13. Weydert JA, Shapiro DE, Acra SA, et al. Evaluation of guided imagery as treatment for recurrent abdominal pain in children: a randomized controlled trial. *BMC Pediatr* 2006;6:29.
14. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SC, et al. Hypnotherapy for children with function abdominal pain or irritable bowel syndrome: a randomized controlled trial. *Gastroenterology* 2007;133:1430–6.

Complementary Therapies for Pediatric Functional Gastrointestinal Disorders

Arine M. Vlieger* and Marc A. Benninga†

*Department of Pediatrics, St. Antonius Hospital, Nieuwegein, The Netherlands, and †Department of Pediatric Gastroenterology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, The Netherlands

Complementary medicine (CM) is defined as ''diagnosis, treatment, and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine'' (1), a definition adopted by the Cochrane Collaboration. CM incorporates many different approaches and methodologies, ranging from ancient techniques such as acupuncture and ayurvedic medicine to chiropractics, homeopathy, spiritual healing, and body-mind medicine. CM enjoys significant popularity among pediatric gastroenterology patients, with a 1-year prevalence of CM use of 36% to 41% (2–4). CM is especially used by children who experience adverse effects of allopathic medication, have school absenteeism, and have low perceived effect of conventional treatment (4). Because of this high prevalence and the fact that some complementary therapies are not without adverse effects and may interfere with

Address correspondence and reprint requests to Dr A.M. Vlieger, Dept of Pediatrics, St Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, The Netherlands (e-mail: arine@vlieger.nl).

The authors report no conflicts of interest.

allopathic medications, it is important for pediatricians and gastroenterologists to become familiar with these therapies. Commonly used complementary therapies in functional gastrointestinal disorders (FGIDs) are herbal medications, massage therapy, acupuncture, and hypnotherapy. All 4 modalities will be discussed briefly.

Herbals and botanicals have been used for hundreds of years for GI complaints in both adults and children, but good scientific evidence of their effectiveness is sparse. Two of 3 randomized controlled trials demonstrated that Chinese herbal medicine may offer improvement in some adults with irritable bowel syndrome (IBS), and a superior posttreatment effect was found with individualized formulations in comparison to standardized preparations (5–7). Peppermint, which is commonly found in over the counter preparations for IBS, has also been found effective (8). The mechanism of action is thought to come from the menthol component of peppermint that relaxes GI smooth muscle by blocking calcium channels (9). In children with IBS the use of peppermint oil seems to be both safe and beneficial; in a small randomized, double-blind controlled 2-week trial 76% of the patients receiving enteric-coated peppermint oil capsules reported a decrease in symptom severity versus only 19% in the placebo group (10). Another popular herb is ginger (*Zingiber officinale*), used especially by patients with nausea and dyspepsia as 1 of the main complaints. It has a prokinetic action, probably mediated by spasmolytic constituents of the calcium antagonist type (11). Ginger has been proven effective for reducing postoperative nausea and vomiting (12) and nausea in early pregnancy (13). It seems to be relatively safe, although abdominal discomfort has been noted in some patients. Despite the fact that herbs are popular in the self-management of childhood constipation, no good randomized controlled trials exist on its use. A recent observational study investigated the use of a Japanese herbal medicine in 15 severely constipated children. It had a favorable clinical effect on constipation and anorectal manometry showed an improvement in rectal reservoir functions (14).

Massage therapy is a commonly used CM modality in patients with chronic disorders. Its use is based among others on the assumption that massage may reduce excitation of visceral afferent fibers and possibly affect central pain perception and processing. Recently it was shown that massage can also increase vagal tone and gastric motility (15). It is therefore reasonable to assume that (abdominal) massage can play a role in GI disorders. A review of 4 controlled trials of abdominal massage for chronic constipation concluded that massage therapy could be a promising treatment for chronic constipation, but more rigorous trials should evaluate its true value (16). Awaiting these trials, many pediatricians advocate its use in children with constipation for promoting bowel activity and relaxing the abdominal wall (17). Reflexology is a special form of massage in which manual pressure is applied to specific zones of the feet that are believed to correspond to different areas of the body, thereby effecting therapeutic change. In adults with IBS a small, single-blind trial did not show any benefit of reflexology foot massage on abdominal pain, defecation frequency, and abdominal distension (18). Bishop et al carried out an observational study in 50 children ages 3 to 14 years who had chronic constipation and/or encopresis. Six sessions of 30 min of reflexology treatment resulted in an increase in bowel movements and a decrease in fecal incontinence episodes (19).

Acupuncture is part of traditional Chinese medicine and has become popular in Western countries in the last several decades. Animal studies have shown an effect for acupuncture on acid secretion, GI motility, and visceral pain (20). Furthermore, it is known that acupuncture and acupressure ameliorate postoperative nausea (21). These findings suggest that acupuncture also may be effective for FGIDs, but results of randomized controlled trials have been disappointing so far. Mixed results were found on the effect of acupuncture on rectal sensations in patients with IBS and no effect was seen on their quality of life and symptom scores (22–24). To date, no good studies have been performed examining the benefits of acupuncture in children with FGIDs. Only one small non-controlled study examined the effect of acupuncture in 17 children with constipation. An increase in bowel movements was found from 1.4 to 5 per week (25).

Finally, gut-directed hypnotherapy (HT) has been shown to be effective in the treatment of adult patients with motility disorders such as IBS, functional dyspepsia, and noncardiac chest pain, with the majority of patients showing long-term improvement in symptoms and quality of life (26–28). Recently, we compared the effect of HT in the treatment of 53 children with long-lasting complaints of functional abdominal pain and IBS with that of standard medical therapy (SMT), consisting of education, dietary interventions, and intervention on stress factors. HT was highly superior, with a significantly greater reduction in pain scores compared to SMT ($P < 0.001$). At 1-year follow up, successful treatment was accomplished in 85% of the HT group and 25% of the SMT group ($P < 0.001$) (29). Hypnosis has also been described as an adjunct in the treatment of children with severe constipation, but trials need to examine its effectiveness (30).

In conclusion, some complementary therapies and especially HT show considerable promise in the treatment of children with FGIDs. Because so many patients are using CM and because some of these modalities are not devoid of risks, it is clear that more research is needed to examine both efficacy and safety of complementary therapies.

REFERENCES

1. Ernst E, Resch K, Mills S, et al. Complementary medicine—a definition. *Br J Gen Pract* 1995;45:506.
2. Day AS. Use of complementary and alternative therapies and probiotic agents by children attending gastroenterology outpatient clinics. *J Paediatr Child Health* 2002;38:343–6.
3. Heuschkel R, Afzal N, Wuerth A, et al. Complementary medicine use in children and young adults with inflammatory bowel disease. *Am J Gastroenterol* 2002;97:382–8.
4. Vlieger AM, Blink M, Tromp E, et al. The use of complementary and alternative medicine in pediatric patients with functional and organic gastrointestinal diseases: results from a multi-center survey. *Pediatrics* 2008;128:e446–51.
5. Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA* 1998;280:1585–9.
6. Madisch A, Holtmann G, Plein K, et al. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. *Aliment Pharmacol Ther* 2004;19:271–9.
7. Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. *Am J Gastroenterol* 2006;101:1574–80.
8. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol* 1998;93: 1131–215.
9. Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. *Gastroenterology* 1991;101:55–65.
10. Kline RM, Kline JJ, Di PJ, et al. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. *J Pediatr* 2001;138:125–8.
11. Ghayur MN, Gilani AH. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. *Dig Dis Sci* 2005;50: 1889–97.
12. Chaiyakunapruk N, Kitikannakorn N, Nathisuwan S, et al. The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obstet Gynecol* 2006;194: 95–9.
13. Borrelli F, Capasso R, Aviello G, et al. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. *Obstet Gynecol* 2005;105:849–56.
14. Iwai N, Kume Y, Kimura O, et al. Effects of herbal medicine Dai-Kenchu-to on anorectal function in children with severe constipation. *Eur J Pediatr Surg* 2007;17:115–8.
15. Diego MA, Field T, Hernandez-Reif M. Vagal activity, gastric motility, and weight gain in massaged preterm neonates. *J Pediatr* 2005;147:50–5.
16. Ernst E. Abdominal massage therapy for chronic constipation: a systematic review of controlled clinical trials. *Forsch Komplementarmed* 1999;6:149–51.
17. Culbert TP, Banez GA. Integrative approaches to childhood constipation and encopresis. *Pediatr Clin North Am* 2007;54: 927–47.
18. Tovey P. A single-blind trial of reflexology for irritable bowel syndrome. *Br J Gen Pract* 2002;52:19–23.
19. Bishop E, McKinnon E, Weir E, et al. Reflexology in the management of encopresis and chronic constipation. *Paediatr Nurs* 2003;15:20–1.
20. Takahashi T. Acupuncture for functional gastrointestinal disorders. *J Gastroenterol* 2006;41:408–17.
21. Ezzo J, Streitberger K, Schneider A. Cochrane systematic reviews examine P6 acupuncture-point stimulation for nausea and vomiting. *J Altern Complement Med* 2006;12:489–95.
22. Rohrbock RB, Hammer J, Vogelsang H, et al. Acupuncture has a placebo effect on rectal perception but not on distensibility and spatial summation: a study in health and IBS. *Am J Gastroenterol* 2004;99:1990–7.
23. Xing J, Larive B, Mekhail N, et al. Transcutaneous electrical acustimulation can reduce visceral perception in patients with the irritable bowel syndrome: a pilot study. *Altern Ther Health Med* 2004;10:38–42.
24. Schneider A, Enck P, Streitberger K, et al. Acupuncture treatment in irritable bowel syndrome. *Gut* 2006;55:649–54.
25. Broide E, Pintov S, Portnoy S, et al. Effectiveness of acupuncture for treatment of childhood constipation. *Dig Dis Sci* 2001;46:1270–5.
26. Jones H, Cooper P, Miller V, et al. Treatment of non-cardiac chest pain: a controlled trial of hypnotherapy. *Gut* 2006;55:1403–8.
27. Calvert EL, Houghton LA, Cooper P, et al. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastroenterology* 2002;123:1778–85.
28. Gholamrezaei A, Ardestani SK, Emami MH. Where does hypnotherapy stand in the management of irritable bowel syndrome? A systematic review. *J Altern Complement Med* 2006;12:517–27.
29. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SC, et al. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: a randomized controlled trial. *Gastroenterology* 2007;133:1430–6.
30. Olness K. Autohypnosis in functional megacolon in children. *Am J Clin Hypn* 1976;19:28–32.

NIH Funding Opportunities for Functional Bowel Disorders in the Pediatric Age Group

Frank A. Hamilton

Chief, Digestive Disease Programs, Division of Digestive Diseases and Nutrition, National Institute of Diabetes, Digestive and Kidney Disease, National Institutes of Health, Bethesda, MD

Address correspondence and reprint requests to Frank A. Hamilton, MD, MPH, Digestive Diseases Program, NIDDK, NIH, 6707 Democracy Blvd, Room 669, Bethesda, MD 20892-5450 (e-mail: fh14e@ nih.gov).

The views expressed are those of the author and do not reflect the position of the National Institutes of Health or the US Department of Health and Human Services.

The author reports no conflicts of interest.

Functional abdominal pain is part of the functional gastrointestinal disorders (FGIDs) that are chronic in

nature and are prevalent in the pediatric population (1). It has been estimated that chronic abdominal pain occurs in 2 to 4% of all pediatric office visits. Hyams found that 13% of middle school–age and 17% of high school–age students experience abdominal pain weekly (2). Because these conditions affect an individual during a critical phase of growth and development, families are confronted with the need and the desire to obtain an explanation for the causes of abdominal pain in their children. These evaluations may be costly without demonstrable evidence of a pathological condition such as an anatomic, metabolic, infectious, inflammatory, or neoplastic disorder. In addition, the chronic nature of abdominal pain has a negative impact on the quality of life for these children (1,3).

During the last 2 decades, there has been an increasing recognition of the impact of functional gastrointestinal disorders in adults along with enhanced research effort to understand the physiological and psychosocial bases of these disorders. The research in functional gastrointestinal disorders in the pediatric age group has, however, lagged. Because collaboration in the field of functional abdominal pain in the pediatric age group is essential to advance research in this area, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) cosponsored a 1-day symposium with the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) on new insights into functional abdominal pain and irritable bowel syndrome. The purpose of the symposium was fourfold: identify research targets for future studies of pediatric FGIDs, foster interaction and information sharing among national and international experts in a variety of relevant disciplines, define the state of the art in the evaluation and treatment of these disorders, and establish a consortium for multidisciplinary collaborative studies.

During the symposium, the role of the National Institutes of Health (NIH) and research opportunities were identified. Twenty-seven institutes and centers within the NIH carry out the NIH's mission to improve the health of the country. Although NIDDK is the lead NIH institute that conducts research on digestive diseases, there are 9 other institutes that conduct research on digestive diseases. Several institutes conduct research on mechanisms and treatment of functional abdominal pain: the National Institute of Child Health and Human Development (NICHD), National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of Mental Health (NIMH), and National Institute of Neurological Disorders and Stroke (NINDS).

NIDDK, NICHD, NCCAM, NIMH, and NINDS have supported research through the NIH's primary mechanism of support, the regular research grant mechanism, the RO1. The use of the RO1 mechanism by investigators has allowed them to unravel the underlying mechanisms of FGIDs. For example, several NIH-supported investigators have provided insights into the link between brain–gut and serotonin interaction in modulating pain perception in abdominal pain (4). Thus, NIH encourages investigators to become aware of funding opportunities that are published weekly in the *NIH Guide*. These funding opportunities may be in the form of program announcements (PA) or Request for Applications (RFA). These funding opportunities highlight the areas that the NIH has defined as priority areas for research.

The Functional Bowel Disorders Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition meeting stated that there is an urgent need for clinical studies and clinical trials in the area of functional abdominal pain in the pediatric population (5). In addition, they recommended the development of therapeutic agents to modulate the abnormalities in the sensorimotor function of the enteric nervous system in functional disorders to relieve specific symptoms that affect these children (6). To support the working group's recommendations, the NIDDK recently released the NIDDK Multicenter Clinical Study Implementation Planning Grant (U34). This mechanism, which is a 2-phase process, should help accelerate research in functional abdominal pain in children and is designed to permit early peer review of the rationale for the proposed clinical study, permit assessment of the design/protocol of the proposed study, provide support for the development of a complete study protocol and associated documents including a manual of operations, and support the development of other essential elements required for the conduct of a clinical study. The completion of the required products of a U34 grant is a prerequisite for submission of a multicenter clinical study cooperative agreement (U01) application (the second part of the process), which will support the actual conduct of the study (7).

NIDDK will accept, send out for peer review, and consider for funding applications for investigator-initiated, multicenter clinical studies from U34 awardees only, except when an exemption from this requirement has been obtained from NIDDK. An applicant who can demonstrate that all of the work required for submission of a multicenter clinical study proposal has been completed may request an exemption from the prerequisite of holding an U34 award before submitting the U01 application (8).

The materials developed in the U34 phase will allow the applicant to initiate study staff training followed by study subject recruitment soon after an expedited peer review and final NIDDK approval of the clinical study application. In order not to delay the initiation of the study, the peer review and award of grant should be completed within 4 months of the receipt of the application, when possible.

INCLUSION OF CHILDREN IN BIOMEDICAL RESEARCH

Aware that research in the area of disorders of children lagged far behind that in adults, the NIH has developed a policy for the inclusion of children in research. This policy was put into place after a jointly sponsored workshop by the NICHD and the American Academy of Pediatrics. The group concluded that there is a need to enhance the inclusion of children in clinical research. This conclusion was based upon scientific evidence, information demonstrating human need, and considerations of justice for children in receiving adequately evaluated treatments. The need reaches across a broad spectrum of disorders for which clinical research is needed, including studies on pharmaceutical and therapeutic agents; behavioral, developmental, and life cycle issues including childhood antecedents of adult disease; and prevention and health services research.

It is NIH policy that children (ie, individuals younger than 21 years) must be included in all human subjects' research that is conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all NIH-conducted or -supported research involving human subjects, including research that is otherwise ''exempt'' in accord with Sections 101(b) and 401(b) of Title 45 of the *Code of Federal Regulations*, Part 46, Protection of Human Subjects. The inclusion of children as subjects in research must be in compliance with all applicable subparts of 45 CFR 46, as well as with other pertinent federal laws and regulations (9). Therefore, proposals for research involving human subjects must include a description of plans for including children. If children will be excluded from the research, then the application or proposal must present an acceptable justification for the exclusion.

These guidelines reaffirm the commitment of the NIH to the fundamental principles of inclusion of children in research. This policy should result in a variety of new research opportunities to address significant gaps in knowledge about health problems, especially the condition of functional abdominal pain and irritable bowel syndrome in the pediatric age group.

CONCLUSIONS

During the last 2 decades, the NIH has taken steps to accelerate research in the area of pediatric disorders, including functional abdominal disorders. The pediatric research community is encouraged to take advantage of the funding opportunities that are periodically advertised in the *NIH Guide*. Furthermore, the pediatric research community is encouraged to take advantage of the U34 mechanism that NIDDK has launched to promote collaborative research in FGIDs.

REFERENCES

1. American Academy of Pediatrics, Subcommittee on Chronic Abdominal Pain, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Chronic abdominal pain in children. Pediatrics 2005;115:e370–e381.
2. Hyams JS. Recurrent abdominal pain and irritable bowel syndrome in children. *J Pediatr Gastroenterol Nutr* 1997;25 (Suppl 1):S16–7.
3. Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123:2108–31.
4. Cooke HJ. Role of the ''little brain'' in the gut in water and electrolyte homeostasis. *FASEB J* 1989;3:127–38.
5. Hyams J, Colletti R, Faure C, et al. Functional gastrointestinal disorders: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2002;35 (Suppl 2):S110–7.
6. Veldhuyzen van Zanten SJ, Talley NJ, Bytzer P, et al. Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999;45 (Suppl 2):II69–77.
7. NIDDK Multi-Center Clinical Study Implementation Planning Grants (U34), NIDDK PAR-08-057. *NIH Guide*, December 18, 2007.
8. NIDDK Multi-Center Clinical Study Cooperative Agreement (U01), PAR-08-058. *NIH Guide*. December 19, 2007.
9. National Institutes of Health Revitalization Act. Pub L No. 103-43, 107 Stat 126 (1993).

Pharmaceutical Industry in Pediatric Drug Development: Partners and Collaborators With Academia and the FDA

Andrew E. Mulberg

Compound Development Team Leader, Clinical Leader, Internal Medicine Portfolio, Mature Products, Johnson&Johnson Pharmaceutical Research and Development, Titusville, NJ

Address correspondence and reprint requests to Andrew E. Mulberg, MD, FAAP, CPI, Johnson&Johnson Pharmaceutical Research and Development, 1125 Trenton Harbourton Rd, E12106, Titusville, NJ 08560 (e-mail: AMulberg@PRDUS.JNJ.com).

Dr Mulberg is a full-time employee of Johnson&Johnson Pharmaceutical Research and Development, LLC.

Even in the so-called developed world, there are significant unmet medical needs for both adults and children.

The history of drug development is clearly one of neglecting the specific needs of children by assuming, incorrectly, that adult data can be directly applied to children. Shirkey has described infants and children as ''therapeutic orphans,'' attesting to the fact that drugs are not often developed for their specific and unmet medical needs (1). Drugs are used in children every day with little guidance on appropriate dosing based on a lack of understanding of the pathobiology, metabolic and physiological differences, and developmental changes that characterize the differences from the adult. Adverse drug reactions or decreased efficacy in children occurs because of inherent over- or underdosing and unrecognized drug–drug interactions in the pediatric patient.

For nearly 4 decades the importance of including children in clinical research and meeting the challenges posed by pediatric drug development has been part of a public debate led chiefly by those advocating for children's improved access to health care. The failure to involve children in this research has resulted in catastrophic misdosing of children based on estimating doses in addition to withholding important therapies in children because the paucity of information does not allow accurate assessment of risk/benefit. The government and regulatory authorities have created an evolving infrastructure through effective legislation that mandates as well as provides incentives for industry to include children in clinical development of new products. There is a notable lack of appropriately labeled drugs for the pediatric population for multiple therapeutic areas, including gastrointestinal diseases.

The Best Pharmaceutical Act for Children (better known as ''pediatric exclusivity'') and the Pediatric Research Equity Act (also known as ''the pediatric rule'') have been legislated to correct the deficiency. Similar laws have been approved in Europe and Canada and are being explored in Japan (personal communication, Hidefumi Nakamura, National Center for Child Health and Development, Tokyo). Involvement of children in clinical development of pharmaceuticals is and will continue to be a standard practice in the industry.

STAKEHOLDERS

Food and Drug Administration

The recent Best Pharmaceutical for Children Act pediatric exclusivity statistics (March 2007) listed products for which Food and Drug Administration (FDA) Requested Studies (*http://www.fda.gov/oc/opt/default.htm*): (N = 341). In addition, the FDA has detailed products for studies submitted for label changes (N = 150), and label changes granted (N = 128). Drugs with pediatric labeling included N = 11 (8.6%) in drug classes for treatment of hypercholesterolemia, acid blockade therapy, inflammatory bowel disease, vomiting, and hepatitis B and C (2). The Critical Path Initiative in 2006 sponsored by the FDA called for targeted research in 6 areas to stimulate the drug and device pipeline (3). Development of biomarkers to more rapidly and/or more efficiently determine the benefit/risk profile of a new therapy included genomic tests to identify patients at high risk for serious toxicity, markers of drug metabolism to individualize drug dosage, and new imaging techniques to assess treatment efficacy. The qualification of new surrogate endpoints, a subset of biomarkers targeted at later phase clinical trials, was identified as an important area to drive more rapid drug development. Surrogate endpoints hold great promise for improving efficiency in clinical research, and incorporating surrogate endpoints could accelerate development in pediatric therapies. Of importance is the notable decrease (as of 2003) in submitted new drug applications to FDA for approval (3). The factors underlying the paucity of new submissions and approvals are multidimensional. A renewed commitment to identify appropriate drug candidates and process toward approval for children is needed.

Pharmaceutical Industry

A pharmaceutical industry stakeholder focused on developing novel targeted therapies and different treatment concepts for a dysfunctional gastrointestinal tract is Movetis (personal communication, Dirk Reyn, PhD, CEO). Several of the targets under investigation have been characterized, including the $5HT_4$ agonists and antagonists, and the $5HT_{1A}$ and $5HT_3$ agonists, which affect gastric emptying, lower esophageal sphincter function, colonic transit, and small bowel motility. The company has reported progress in phase I through III development.

Academic Community

The pediatric academic community has been fostering more effective collaborations in various efforts, including the programs linked to hepatitis C and biliary atresia, sponsored through the National Institutes of Health. Other potential areas affecting drug development are the development and approvability of appropriate surrogate markers for gastrointestinal diseases. Examples of surrogate markers that need further investigation are patient-related outcome measures for diseases, including gastroesophageal reflux disease (GERD), irritable bowel syndrome, and other functional bowel disorders. Significant progress toward patient-related outcomes for GERD has been made especially through the work of Dr Susan Orenstein, in partnership with Johnson&Johnson developing I-GERQ-R as a validated tool, and Wyeth Pharmaceuticals in developing GASP-Q for GERD. In the author's opinion, developing better surrogate markers for other gastrointestinal diseases could accelerate the

availability of new treatments for children with gastrointestinal diseases.

CONCLUSIONS

Why have these issues been ignored and what accounts for the changing environment? In part, the economics of drug development and a narrow interpretation of the ''ethics'' of drug development in children dictated that despite the rare occasions of specific agents developed for niche diseases, first indications would be in adult patients. Due to a ''perfect storm'' of regulatory guidances, interest in academia from pediatric experts, and an evolving pediatric-focused workforce in industry that understands the business case for proper drug development for drugs for children, the tide may be changing. Targeting the needs of children is an important task in all societies in which the impact of using proper therapies proven to be safe and effective has significant medical economic consequences. Nelson Mandela said, ''There can be no keener revelation of a society's soul than the way in which it treats its children.'' FDA, academia, and the pharmaceutical industry must remain active and vigorously enthusiastic collaborative partners to yield safe and effective drugs for patients with gastrointestinal diseases. Let us hold hands more effectively and all will benefit, especially children, from our focus on gastrointestinal disease.

REFERENCES

1. Shirkey H. Editorial comment: therapeutic orphans. *J Pediatr* 1968;72:119–20.
2. US Food and Drug Administration. Office of Pediatric Therapeutics. *http://www.fda.gov/oc/opt/default.htm*. Accessed September 2007.
3. US Food and Drug Administration. FDA's critical path initiative. *http://www.fda.gov/oc/initiatives/criticalpath*. Accessed September 2007.

Organization of a Research Consortium: The Time Is Now

Jeffrey S. Hyams

Head, Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children's Medical Center, Hartford

In 1958 Apley and Naish published their seminal article on recurrent abdominal pain of childhood (RAP) (1) and suggested that worry and excitement were common features in children with this problem. The implication that psychological abnormalities were the cause of the pain created a pejorative atmosphere for decades to come as children with chronic abdominal pain in whom no obvious disease was present were considered to have primarily mental health issues. The severity of the pain was often questioned by both their parents and their physicians because no disease was present. RAP became a diagnostic endpoint, often after extensive and fruitless investigation, and families were essentially told that nothing was wrong with their child.

In 1994 the first edition of *The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment. A Multinational Consensus* (2) was published, describing symptom-based criteria for functional gastrointestinal disorders (FGIDs) in adults. These criteria were largely arrived at by a consensus of experts in the field who recognized the limitations of published studies but who also set forth a framework for further study. In 2000 the second edition of this text was published (3). It contained a chapter on pediatric FGIDs written by 7 pediatric gastroenterologists who used limited published data, and mostly their own experience, to describe 13 functional pediatric disorders ranging from infant regurgitation to abdominal pain to diarrhea and constipation. The field of pediatric FGIDs took on some order. In 2006 the third and most recent edition of this text was published (4) by 13 authors who considered the topic of pediatric FGIDs so broad that they divided their efforts into 2 chapters focusing on infant/toddler issues in one and child/adolescents in the other. The authors of the pediatric chapters in the third edition cited 332 references compared with only 107 for the authors of the second edition. Finally some data were available to support descriptions and potential pathophysiology and treatment of FGIDs, but almost all of the reports were of small numbers of patients and usually from a single center.

Address correspondence and reprint requests to Jeffrey S. Hyams, MD, Connecticut Children's Medical Center, 282 Washington St, Hartford, CT 06106 (e-mail: jhyams@ccmckids.org).

The author reports no conflicts of interest.

Although clearly, pediatric FGIDs were now a topic of legitimate research interest, they still did not command multicenter investigation.

NEED FOR COLLABORATION

Pediatric FGIDs constitute the bulk of pediatric gastroenterology practice as well as demand considerable attention from primary pediatric providers. With increasing knowledge of the role of the enteric nervous system and its relation to the central nervous system, as well as tools to study physiological responses (eg, barostat, brain imaging), the time to collaboratively study these disorders has arrived. Moreover, no single center can study natural history or perform adequately powered intervention trials. It is time to work together.

WHAT DO WE STUDY?

If a collaborative research group to study pediatric FGIDs is formed, it will need to carefully choose its priorities. A broad, unattainable agenda will only lead to failure and frustration; however, clearly defined and reachable goals will facilitate success and provide energy for further collaboration. The natural history of well-defined pediatric FGIDs is a relatively easy target for a multicentered approach. Drug trials and genetic studies of pediatric FGIDs (eg, serotonin transporter gene polymorphisms) are also achievable targets that will require multi-centered studies.

Investigators into FGIDs should be heartened by the precedent of collaboration among pediatric oncologists who eventually formed the Clinical Oncology Group, pediatric rheumatologists who formed a multicentered research group, and pediatric gastroenterologists who formed several productive research consortia to study inflammatory bowel disease, eosinophilic esophagitis, and biliary atresia. The lesson to be learned from all of these groups is that early cooperation is better than competition. It would serve pediatric FGID research well if 1 study group were formed rather than several.

WHO SHOULD PARTICIPATE?

An interest in pediatric FGIDs is the basis for participation in research studies but will likely not be sufficient as the only criterion of participation. The ability of an investigator/center to participate will also depend upon time and personnel. Pediatric gastroenterologists are increasingly busy with clinical productivity demands, administrative burdens, educational activities, and their personal lives. Asking busy clinicians to direct institutional review board submissions for drug trials or document natural history events in patients with FGIDs is bound to fail. Dedicated time and research personnel are required for these tasks and funds to support them may be difficult to identify at first. Commitment to success is required for participation.

WHO WILL FUND THIS?

It is unlikely that funds will initially be available to support a large network of primary investigators and research assistants. More likely, centers with investigators with an ability to carve out some time as well as existing personnel that can assist with studies will be required. That does not mean that smaller centers will not be able to participate, but it is likely that at first any investigator/center will need to provide their own resources. Large-scale drug trials will likely be supported by the pharmaceutical industry and reimbursement for time and effort will be straightforward.

Although grassroots or self-funding may help a collaborative group get started, it will not be sustainable under this model. Initial success in forming a collaborative group and demonstrating productivity must lead to application for private or federal funding. Another potential scenario is a partnership between the collaborative group and the pharmaceutical industry. Although this may well be a productive relationship, care must be taken to ensure that the collaborative group remains independent in its mission, leadership structure, and ownership and publication of gathered data.

HOW WILL SUCCESS BE MEASURED?

Publication of high-quality peer-reviewed data will be the primary outcome measure of any collaborative research group. The group must form a publication committee that will consider hypothesis-driven research proposals, review analysis of data, perform critique of manuscripts, and approve any submission from a member of the group. Criteria for authorship must be established early to give appropriate credit to those who make meaningful contributions to any project. A second goal of the group must be to facilitate education of medical personnel and the lay public in pediatric FGIDs. The quality of life of these children will be improved by a better understanding of both communities.

INITIAL STEPS

The next year should provide ample time for the establishment of a leadership structure for a pediatric FGID collaborative group. During that time the leadership should actively recruit suitable participating centers and identify 1 or 2 focused, easily accomplished projects. Lines of communication, data-reporting methodology, statistical infrastructure, publication oversight, and a meeting schedule should be established. Preliminary discussions should take place to identify possible funding mechanisms.

The time has come to move from expert opinion to hard data to guide our clinical care. It is time to provide the evidence so that we can truly practice evidence-based medicine.

REFERENCES

1. Apley J, Naish N. Recurrent abdominal pains: a field survey of 1,000 school children. *Arch Dis Child* 1958;33:165–70.
2. Drossman D, Richter J, Talley N, et al. The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment. A Multinational Consensus. McLean, VA: Degnon Associates; 1994.
3. Drossman D, Corazziari E, Talley N, et al. The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment. A Multinational Consensus. 2nd ed. McLean, VA: Degnon Associates; 2000.
4. Drossman D, Corazziari E, Talley N, et al. The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment. A Multinational Consensus. 3rd ed. McLean, VA: Degnon Associates; 2006.