INTRODUCTION

The Functional Gastrointestinal Disorders and the Rome III Process

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Throughout recorded history, and alongside structural diseases of the intestinal tract, are maladies that have produced multiple symptoms of pain, nausea, vomiting, bloating, diarrhea, constipation, or difficult passage of food or feces.[1] Although structural diseases can be identified by pathologists and at times cured by medical technology, the nonstructural symptoms that we describe as "functional" remain enigmatic and less amenable to explanation or effective treatment. Often considered "problems of living," there are physiological, intrapsychic, and sociocultural factors that amplify perception of these symptoms so they are experienced as severe, troublesome, or threatening, with subsequent impact on daily life activities. Those suffering from such symptoms attribute them to an illness and self-treat or seek medical care. Traditionally trained physicians then search for a disease (inflammatory, infectious, neoplastic and other structural abnormalities) in order to make a diagnosis and offer treatment specific to the diagnosis. In most cases,[2] no structural etiology is found, the doctor concludes that the patient has a "functional" problem, and the patient is evaluated and treated accordingly.

This clinical approach results from a faulty conceptualization of functional gastrointestinal disorders (FGIDs) and in the inaccurate, demeaning and potentially harmful implications that some physicians, patients, and the general public attribute to them.[3] Some clinicians feel ill at ease when making a diagnosis of an FGID because they are trained to seek pathology.[4] In a random sample survey of 704 members of the American Gastroenterological Association,[5] the most common endorsement of a functional gastrointestinal (GI) disorder was " . . .. no known structural (ie, no pathological or radiological) abnormalities, or infectious, or metabolic causes" (81%). Next came "a stress-disorder" (57% practitioners and 34% academicians and trainees), and last was a "motility disorder" (43% practitioners and 26% academicians/trainees.[6] A more recent survey of international investigators agreed that in their countries, physicians view the FGIDs as psychological disorders or merely the absence of organic disease and often ascribe pejorative features to the patient.[3] Some physicians deny the very existence of the functional GI disorders,[7] whereas others exhibit dismissive or negative attitudes toward patients.[4,8,9] Some physicians may pursue unneeded diagnostic studies to find something "real",[10] resulting in increased health care costs and possibly inappropriate care.[11] These types of beliefs and behaviors can "delegitimize" the FGIDs and the patients who experience them.

What is missing in these attitudes and behaviors is a proper understanding of the true genesis of FGID symptoms, an acknowledgment of their impact on patients, and a rational basis for diagnosing and treating them. In the last few decades, several important events have occurred that brought these common disorders into the forefront of clinical care, scientific investigation, and public awareness, and in the process, have made them scientifically exciting and clinically legitimate.

The first event began 3 decades ago with a paradigm shift that moved away from conceptualizing illness and disease based on a 3-century-old reductionistic model of disease in which the effort was to identify a single underlying biological etiology to a more integrated, biopsychosocial model of illness and disease.[12–14] The former disease-based model had its roots with Descartes' separation of mind and body and at the time was a concept that harmonized prevailing societal views of separation of church and state.[1,13] What resulted was permission to dissect the human body (which was previously forbidden), so disease was defined by what was seen (ie, pathology based on abnormal morphology). This approach led to centuries of valuable research producing effective treatments for many diseases. The concept of the mind (ie, the central nervous system [CNS]) as being amenable to scientific study or as playing a role in illness and disease was marginalized, however. The mind was considered the seat of the soul, not to be tampered with. This idea seems to have had a profound effect on Western

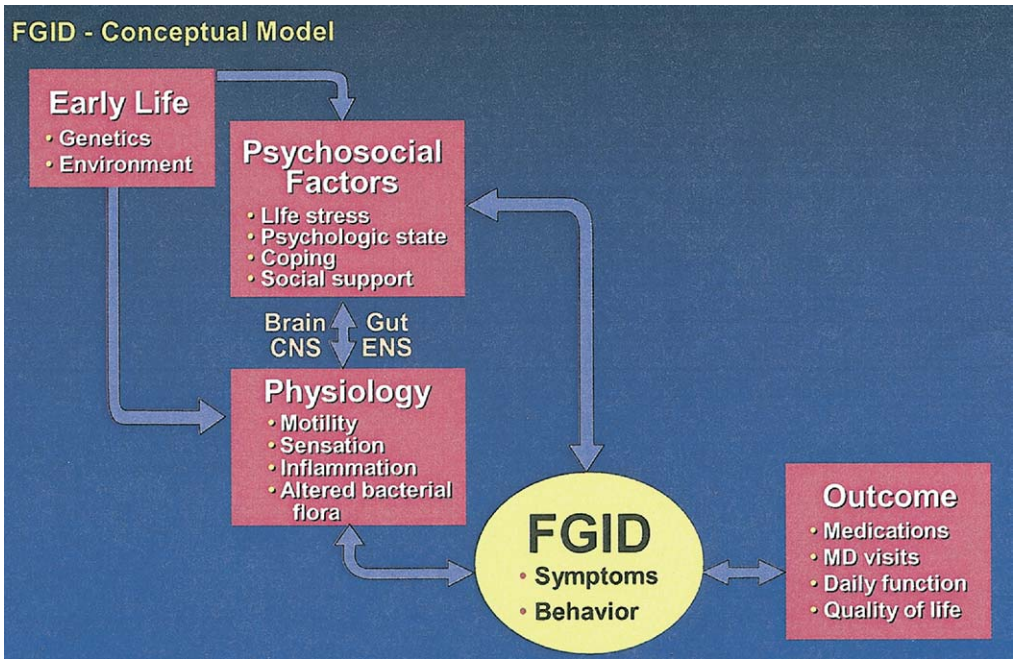

Figure 1. This biopsychosocial conceptualization of the pathogenesis and clinical expression of the functional GI disorders shows the relationships between psychosocial and physiological factors, functional GI symptoms, and clinical outcome.

society where mental illness or even the effects of stress on physiological function became less available for study and even stigmatized. More recent scientific studies link the mind and body as part of a system where their dysregulation can produce illness (the person's experience of ill health) and disease. By embracing this integrated understanding, the biopsychosocial model allows for symptoms to be both physiologically multidetermined and modifiable by sociocultural and psychosocial influences.

Figure 1 illustrates the relationships between psychosocial and physiological factors and functional GI symptoms and clinical outcome. Early in life, genetics, in addition to environmental factors such as family influences on illness expression, abuse, major losses, or exposure to infections, may affect one's psychosocial development in terms of one's susceptibility to life stress or psychological state and coping skills, as well as susceptibility to gut dysfunction—abnormal motility, altered mucosal immunity, or visceral hypersensitivity. Furthermore, these "brain-gut" variables reciprocally influence their expression. Therefore, an FGID is the clinical product of this interaction of psychosocial factors and altered gut physiology via the brain-gut axis.[15] For example, an individual with a bacterial gastroenteritis or other bowel disorder who has no concurrent psychosocial difficulties and good coping skills may not develop the clinical syndrome (or be aware of it) or if it does develop, may not perceive the need to seek medical care. Another individual with coexistent psychosocial comorbidities, high life stress, abuse history, or maladaptive coping, may develop a syndrome (eg, postinfectious irritable bowel syndrome [IBS] or dyspepsia), go to the physician frequently, and have a generally poorer outcome.[16–20] Furthermore, the clinical outcome will, in turn, affect the severity of the disorder (note double-sided arrow in Figure 1). Thus, a family that addresses the illness behavior adaptively and attends to the individual and his or her psychosocial concerns may reduce the impact of the illness experience and resultant behaviors. Conversely, a family that is overly solicitous to the person's illness[21] or a societal group that interprets certain symptoms with threat may amplify the symptoms and illness behaviors.[22] In the health care field, when the physician acknowledges the reality of the patient's complaints, provides empathy, and engages in an effective physician-patient interaction, symptom severity and health care seeking are reduced.[23] Conversely, another physician who repeatedly performs unneeded diagnostic studies to rule out pathological disease, dismisses the patients concerns, or does not effectively collaborate in the patient's care is likely to promote a vicious cycle of symptom anxiety and health care seeking.[11,24]

The second change over the last 2 decades has been the remarkable growth in investigative methods that allow us to quantify these associations for the FGIDs. Within the gut, motility assessment has advanced,[25–27] the barostat is the standard for testing visceral hypersensitivity,[28] and the investigation of peptides, mucosal immunology, inflammation, and alterations in the bacterial flora of the gut provide the translational basis for GI symptom generation. With regard to the brain, imaging

methods using positron emission tomography and functional magnetic resonance imaging offer a window into the central modulation of GI function and its linkages to emotional and cognitive areas,[29] whereas more standardized psychological instruments permit the categorization and quantification of emotions, stress, cognitions, and health-related quality of life. The use of these modalities in research is helping us determine their influences on symptoms and health outcomes.

A third event over the last decade has been the development and release of new pharmacological agents to treat the FGIDs. These include 5-HT agonists and antagonists as well as other gut-receptor–active agents for constipation and diarrhea,[30–32] more centrally acting agents to treat stress-mediated effects of CNS modulation of the gut,[33–35] and many others covering a vast array of mechanisms. For better or worse, increasing media attention to these pharmaceutical agents has also heightened awareness of the FGIDs within the medical community and the general public.

We have come a long way since the 1980s. The FGIDs are now recognized as clinical entities. Researchers and clinicians worldwide are more involved with these disorders, and the Rome process has played an important role in the categorization and dissemination of the new and evolving knowledge. The FGIDs are now a prominent part of undergraduate and postgraduate medical curricula, clinical training programs, and international symposia. The number of articles in peer-reviewed journals has skyrocketed, as has attention to these disorders through public media including television and cinema. There are now future challenges to be faced, which include improved understanding of the relationships between the mind and gut, as well as the translation of basic neurotransmitter function into clinical symptoms and their impact on the patient.

The need still remains to educate clinicians and the general public on this rapidly growing knowledge. This edition of GASTROENTEROLOGY is a compilation of the Rome III documents. It provides a basis for understanding the pathophysiological, diagnostic, and treatment aspects of the FGIDs and also includes the new Rome III criteria for diagnosis of adult and pediatric FGIDs. A more detailed review of this field will be provided in the Rome III textbook to be released later this year. We hope the efforts of Rome III provide a valuable resource to clinicians and investigators, ultimately as a means to help our patients and further legitimize these disorders to society.

The following sections summarize the Rome III classification, scientific observations that relate to the FGIDs, a generalized approach to patient care, and finally, a discussion of the rationale and methods of the Rome III process leading to this publication.

The Rome III Classification System FGIDs

The 28 adult and 17 pediatric FGIDs are presented in Table 1. These are symptom-based diagnostic criteria that are not explained by other pathologically based disorders. In recent years, however, histological findings have been identified that blur the distinction between "functional" and "organic."[3,10,36] The FGIDs are better categorized by their motor and sensory physiology and CNS relationships that produce disorders of GI functioning; as such, there can be clinical overlap of FGIDs with other disorders.

The FGIDs are classified into six major domains for adults: esophageal (category A); gastroduodenal (category B); bowel (category C); functional abdominal pain syndrome (FAPS) (category D); biliary (category E); and anorectal (category F). The pediatric system is classified first by age range (neonate/toddler [category G] and child/adolescent [category H]) and then by symptom pattern or area of symptom location. Each category site contains several disorders, each having relatively specific clinical features. So, the functional bowel disorders (category C) include IBS (C1), functional bloating (C2), functional constipation (C3), and functional diarrhea (C4), which anatomically is attributed to the small bowel, colon, and rectum. Although symptoms (eg, diarrhea, constipation, bloating, pain) may overlap across these disorders, IBS (C1) is more specifically defined as pain associated with change in bowel habit, and this is distinct from functional diarrhea (C4) characterized by loose stools and no pain, or functional bloating (C2) when there is no change in bowel habit. Each condition also has different diagnostic and treatment approaches.

The symptoms of the FGIDs relate to combinations of several known physiological determinants: increased motor reactivity, enhanced visceral hypersensitivity, altered mucosal immune and inflammatory function (which includes changes in bacterial flora), and altered CNS-enteric nervous system (ENS) regulation (as influenced by psychosocial and sociocultural factors and exposures). For example, fecal incontinence (category F1) may primarily be a disorder of motor function, whereas FAPS (category D) is primarily understood as amplified central perception of normal visceral input. IBS (category C1) is more complex and results from a combination of dysmotility, visceral hypersensitivity, mucosal immune dysregulation, alterations of bacterial flora, and CNS-ENS dysregulation. The contribution of these factors may vary

Table 1. Rome III Functional Gastrointestinal Disorders

A. Functional esophageal disorders
  A1. Functional heartburn
  A2. Functional chest pain of presumed esophageal origin
  A3. Functional dysphagia
  A4. Globus
B. Functional gastroduodenal disorders
  B1. Functional dyspepsia
    B1a. Postprandial distress syndrome
    B1b. Epigastric pain syndrome
  B2. Belching disorders
    B2a. Aerophagia
    B2b. Unspecified excessive belching
  B3. Nausea and vomiting disorders
    B3a. Chronic idiopathic nausea
    B3b. Functional vomiting
    B3c. Cyclic vomiting syndrome
  B4. Rumination syndrome in adults
C. Functional bowel disorders
  C1. Irritable bowel syndrome
  C2. Functional bloating
  C3. Functional constipation
  C4. Functional diarrhea
  C5. Unspecified functional bowel disorder
D. Functional abdominal pain syndrome
E. Functional gallbladder and Sphincter of Oddi (SO) disorders
  E1. Functional gallbladder disorder
  E2. Functional biliary SO disorder
  E3. Functional pancreatic SO disorder
F. Functional anorectal disorders
  F1. Functional fecal incontinence
  F2. Functional anorectal pain
    F2a. Chronic proctalgia
      F2a1. Levator ani syndrome
      F2a2. Unspecified functional anorectal pain
    F2b. Proctalgia fugax
  F3. Functional defecation disorders
    F3a. Dyssynergic defecation
    F3b. Inadequate defecatory propulsion
G. Functional disorders: neonates and toddlers
  G1. Infant regurgitation
  G2. Infant rumination syndrome
  G3. Cyclic vomiting syndrome
  G4. Infant colic
  G5. Functional diarrhea
  G6. Infant dyschezia
  G7. Functional constipation
H. Functional disorders: children and adolescents
  H1. Vomiting and aerophagia
    H1a. Adolescent rumination syndrome
    H1b. Cyclic vomiting syndrome
    H1c. Aerophagia
  H2. Abdominal pain-related functional gastrointestinal disorders
    H2a. Functional dyspepsia
    H2b. Irritable bowel syndrome
    H2c. Abdominal migraine
    H2d. Childhood functional abdominal pain
      H2d1. Childhood functional abdominal pain syndrome
  H3. Constipation and incontinence
    H3a. Functional constipation
    H3b. Nonretentive fecal incontinence

across different individuals or within the same individual over time. Thus, the clinical value of separating the functional GI symptoms into discrete conditions as shown in Table 1 is that they can be reliably diagnosed and more specifically treated.

Scientific Observations on the Pathophysiology of Functional GI Disorders

Using Figure 1 as a template, the following is a more detailed description of these associations.

Genetic Predispositions

Genetic factors may predispose some individuals to develop FGIDs, whereas in others, environmental factors contribute to the phenomic expression of these conditions, as well as patient attitudes and behaviors (including health care seeking) relating to it. Genetic factors may play a role in several pathways, including lower levels of IL-10—an anti-inflammatory cytokine—in some patients with IBS [37]that may effect gut mucosal neural sensitivity, serotonin reuptake transporter polymorphisms that can effect levels of 5-HT neurotransmitter, or the response to 5-HT blocking agents,[38,39] g-protein polymorphisms that can affect both CNS and gut-related actions,[40] and α2-adrenoreceptor polymorphisms that affect motility.[41] An area for future study is the role of CNS-related genetic abnormalities as identified in other conditions, for instance, with regard to hypothalamic-pituitary-adrenal corticotrophin-releasing hormone reactivity or linkages between IBS and commonly observed co-morbidities such as posttraumatic stress disorder, depression, and anxiety disorders. For example, serotonin reuptake transporter polymorphisms have effects on mood disturbances [42]and may be a genetic link to disorders of brain-gut function such as IBS.

Early Family Environment

The aggregation of FGIDs in families[43] is not only genetic. What children learn from parents may contribute to the risk of developing an FGID.[44] In fact, children of adult patients with IBS make more health care visits (and incur more health care costs) than the children of non-IBS parents.[45,46]

Psychosocial Factors

Although psychosocial factors do not define the FGIDs and are not required for diagnosis, they are modulators of the patient's experience and behavior, and ultimately, the clinical outcome. Research on the psy-

chosocial aspects of patients with FGIDs yields three general observations: (1) Psychological stress exacerbates GI symptoms. Psychological stress affects GI function and produces symptoms in healthy subjects, but does so to a greater degree in patients with FGIDs; (2) Psychosocial factors modify the experience of illness and illness behaviors such as health care seeking. Although patients with FGIDs show greater psychological disturbance than otherwise healthy subjects and patients with medical disease, the data are drawn from patients seen at referral centers. Those with FGIDs who are non–health care seekers do not show these appreciable differences in psychological disturbances from the general population. This explains why psychosocial trauma (e.g., sexual or physical abuse history) is more common in referral centers than in primary care, may lower pain threshold and symptom reporting, and is associated with a poorer clinical outcome. These factors can be reduced or "buffered" by adaptive coping skills and social support, and the psychosocial response of family, society, and culture can also have a palliative effect on the illness experience; (3) A functional GI disorder may have psychosocial consequences. Any chronic illness has psychosocial consequences on one's general well-being, daily function status, one's sense of control over the symptoms, and the implications of the illness in terms of future functioning at work and at home. This is understood in terms of one's health-related quality of life.

Abnormal Motility

In healthy subjects, strong emotion or environmental stress can lead to increased motility in the esophagus, stomach, small intestine, and colon. The FGIDs, however, are characterized by having an even greater motility response to stressors (psychological or physiological) when compared to normal subjects.[26,47–49] These motor responses are partially correlated with bowel symptoms, particularly vomiting, diarrhea and constipation, but are not sufficient to explain reports of chronic or recurrent abdominal pain.

Visceral Hypersensitivity

Visceral hypersensitivity helps explain the poor association of pain with GI motility with many of the functional GI disorders (eg, functional chest pain of presumed esophageal origin [A2], epigastric pain syndrome [B1b], IBS[C1], and FAPS [D]).[50,51] These patients have a lower pain threshold with balloon distension of the bowel (visceral hyperalgesia), or they have increased sensitivity even to normal intestinal function (eg, allodynia), and there may be an increased area of somatic referral of visceral pain. Visceral hypersensitivity may be amplified in patients with FGIDs, a process called *sensitization* or *stimulus hyperalgesia*. Repetitive balloon inflations in the colon lead to a progressive increase in pain intensity that occurs longer and to a greater degree in patients with FGIDs than in controls.[52] Hypersensitivity and sensitization may occur through altered receptor sensitivity at the gut mucosa and myenteric plexis, which may be enabled by mucosal inflammation,[36] degranulation of mast cells close to enteric nerves,[53] or increased serotonin activity,[54,55] possibly enhanced by alteration of the bacterial environment or infection.[56,57] There may also be increased excitability via central sensitization[58] and possibly growth of the spinal cord dorsal horn neurons due to chronic or repetitive visceral stimulation, thus amplifying throughput to the CNS. Finally, there may be altered central downregulation of visceral afferent transmission, thus reducing pain.[29,59]

Inflammation

For almost 15 years, investigators have proposed that increased inflammation in the enteric mucosa or neural plexi may contribute to symptom development,[60] yet only a few years ago was it recognized that about one half of patients with IBS have increased activated mucosal inflammatory cells.[36] This information appears to relate to other clinical observations that about one third of patients with IBS or dyspepsia describe that their symptoms began after an acute enteric infection, and also, up to 25% of patients presenting with an acute enteric infection will go on to develop IBS-like or dyspeptic symptoms[61–63]; the mucosa of these individuals typically have increased inflammatory cells and inflammatory cytokine expression.[17,64] It is likely that mucosal inflammation may, at least in part, be a determinant of visceral hypersensitivity and sensitization as previously noted.

Bacterial Flora

Following from work that addresses a possible role for bacterial overgrowth in some patients with IBS,[65] there is growing interest in the role of altered bacterial flora contributing to the development of IBS. For example,[66] improvement in IBS symptoms in response to *Bifidobacter infantis* was associated with alteration of IL-10/IL-12 ratios, thus converting a more inflammatory cytokine environment seen in IBS to a more normal setting as seen in healthy individuals. Future studies are needed to support this growing area of research in the FGIDs.

Brain-Gut Interactions via the CNS-ENS

Bidirectional "hardwiring" of brain-gut axis. The brain-gut axis allows bi-directional input and thus links emotional and cognitive centers of the brain with peripheral functioning of the GI tract and vice versa. So, extrinsic (vision, smell, etc) or enteroceptive (emotion, thought) information has, by nature of its neural connections from higher centers, the capability to affect GI sensation, motility, secretion, and inflammation. Conversely, viscerotopic effects (eg, visceral afferent communications to the brain) reciprocally affect central pain perception, mood, and behavior. For example, spontaneously induced contractions of the colon in rats leads to activation of the locus coeruleus in the pons, an area closely connected to pain and emotional centers in the brain.[67] Conversely, increased arousal or anxiety is associated with a decrease in the frequency of migrating motor complex activity of the small bowel[68] and of heightened visceral hypersensitivity and autonomic reactivity among patients with IBS.[69]

Stress and postinfectious FGID. A feature of the FGIDs is their increased motor and sensory reactivity to environmental stimuli, which also leads to greater gut physiological reactivity to stress[69] or to its neurochemical mediators such as corticotrophin-releasing hormone.[33,70–72] A good model for brain-gut interactions relates to postinfectious IBS (PI-IBS). In two studies[55,62] that compared patients who develop PI-IBS to those who recover from infection without developing IBS (recovered group) and to a nonsymptomatic control group, the distinguishing features relate to increased mucosal inflammation and higher levels of psychological distress occurring at the onset of the infection. In fact, there were no significant differences in visceral sensation thresholds or motility between the PI-IBS and the recovered group, suggesting that CNS amplification of peripheral signals occurring in the psychologically distressed PI-IBS group raised them to conscious awareness, thereby perpetuating the symptoms.[73] Furthermore, it is possible that the CNS contributed to the increased expression of peripheral inflammatory/cytokine activity via altered hypothalamic-pituitary-adrenal axis reactivity to stress as is seen in IBS.[74] These data suggest that for PI-IBS to become clinically expressed, there must be evidence for brain-gut dysfunction with both visceral sensitization and high levels of psychological distress.

Brain imaging. Brain imaging, using positron emission tomography, functional magnetic resonance imaging, or other modalities[29,75,76] provides an opportunity to assess brain function in response to visceral stimulation[77,78] among healthy subjects and patients with FGIDs. These studies may increase understanding of the role of the CNS in modulating visceral pain and motility. In general, there is an association of anterior cingulate cortex (ACC) activation to rectal distension in IBS relative to controls.[75] Studies using both functional magnetic resonance imaging and positron emission tomography show increases in activity of the ACC compared to controls.[79–84] Preliminary data also show that in IBS, ACC activation to rectal distention correlates with anxiety,[85] stressful life events, maladaptive coping[86] and a history of abuse.[87] Furthermore, abuse history and IBS diagnosis appear to have synergistic effects causing even greater activation of the perigenual ACC.[88] Future studies may help us view the responses to CNS treatments like psychological[89] and antidepressant[90] therapies in IBS, thus predicting agents more amenable to such treatments.

Brain-gut peptides. A treatment approach consistent with the concept of brain-gut dysfunction is likely to involve the neuropeptides and receptors present in the enteric and CNS. Putative agents include primarily 5-HT and its congeners, the enkephalins and opioid agonists, substance P, calcitonin gene-related polypeptide, and cholecystokinin, neurokinin receptor, and corticotrophin-releasing hormone antagonists among others. These neuropeptides have integrated activities on GI function and human behavior depending upon their location. Ongoing phase II and III pharmacological treatment trials using agents active at these receptor sites will hopefully address the diverse, but interconnected symptoms of pain, bowel dysfunction, and psychosocial distress so commonly associated with the FGIDs.

An Approach to the Care of Patients With Functional GI Disorders

This section provides general care guidelines for patients with FGIDs. Further information can be found elsewhere.[91–95]

The Therapeutic Relationship

The basis for implementing an effective physician-patient relationship is supported by growing evidence of improved patient satisfaction, adherence to treatment, symptom reduction, and other health outcomes.[23,95–97] Table 2 provides the guidelines for the establishment of a therapeutic relationship.[98]

Because the FGIDs are chronic, it is important to determine the immediate reasons for the patient's visit: ("What led you to see me at this time?") and to evaluate the patient's verbal and nonverbal communication. Possible causes include: (1) new exacerbating factors (dietary

Table 2. Guidelines to Establish a Therapeutic Physician-Patient Relationship

1. Obtain the history through a nondirective, nonjudgmental, patient-centered interview.
2. Conduct a careful examination and cost-efficient investigation.
3. Determine how much the patient understands about the illness and his or her concerns ("What do you think is causing your symptoms?").
4. Provide a thorough explanation of the disorder that takes into consideration the patient's beliefs.
5. Identify and respond realistically to the patient's expectations for improvement ("How do you feel I can be helpful to you?").
6. When possible, provide a link between stressors and symptoms that are consistent with the patient's beliefs ("I understand you don't think stress is causing your pain, but the pain itself is so severe and disabling that it's causing you a great deal of distress.").
7. Set consistent limits ("I appreciate how bad the pain must be, but narcotic medication is not indicated.").
8. Involve the patient in the treatment ("Let me suggest some treatments for you to consider.").
9. Make recommendations consistent with patient interests ("Antidepressants can be used for depression, but they are also used to "turn down" the pain and in doses lower than that used for depression.").
10. Establish a long-term relationship with a primary care provider.

change, concurrent medical disorder, side effects of new medication), (2) personal concern about a serious disease (recent family death), (3) environmental stressors (eg, major loss, abuse history), (4) psychiatric comorbidity (depression, anxiety), (5) impairment in daily function (recent inability to work or socialize), or (6) a "hidden agenda" such as narcotic or laxative abuse, or pending litigation or disability.

Once the reasons for the visit are determined, treatment may be based on the severity and nature of the symptoms, the physiologic and psychosocial determinants of the patient's illness behavior, and the degree of functional impairment. Although illness severity exists on a continuum, it is arbitrarily separated into mild, moderate, and severe categories.

Mild symptoms. Patients with mild or infrequent symptoms are usually seen in primary care practices and do not have major impairment in function or psychological disturbance. They may have concerns about the implications of their symptoms, but do not make frequent visits and usually maintain normal activity levels. Here, treatment is directed toward:

1. *Education.* Indicate that the FGIDs are very real and the intestine is overly responsive to a variety of stimuli such as food, hormonal changes, medication, and stress. Pain resulting from spasm or stretching of the gut, from a sensitive gut, or both, can be experienced anywhere in the abdomen and can be associated with changes in GI function leading to symptoms (eg, pain, nausea, vomiting, diarrhea). The physician should emphasize that both physiologic and psychological factors interact to produce symptoms.
2. *Reassurance.* The physician should elicit patient worries and concerns and provide appropriate reassurance. This can be an effective therapeutic intervention, but the patient will not accept it if it is communicated in a perfunctory manner and before necessary tests are completed.
3. *Diet and medication.* Offending dietary substances (eg, lactose, caffeine, fatty foods, alcohol, etc.) and medications that adversely cause symptoms should be identified and possibly eliminated. Sometimes a food diary is helpful.

Moderate symptoms. A smaller proportion of patients usually seen in primary or secondary care report moderate symptoms and have intermittent disruptions in activity, for example, missing social functions, work, or school. They may identify a close relationship between symptoms and inciting events such as dietary indiscretion, travel, or distressing experiences. They may be more psychologically distressed than patients with mild symptoms. For this group, additional treatment options are recommended:

1. *Symptom monitoring.* The patient can keep a symptom diary for 1 to 2 weeks to record the time, severity, and presence of associated factors. This diary may help to identify inciting factors such as dietary indiscretions or specific stressors not previously considered. The physician can then review possible dietary, lifestyle, or behavioral influences with the patient. This step encourages the patient's participation in treatment, and as symptoms improve, increases his or her sense of control over the illness.
2. *Pharmacotherapy directed as specific symptoms*. Medication can be considered for symptom episodes that are distressing or that impair daily function. The choice of medication will depend on the predominant symptoms and is outlined in later chapters of this book. In general, prescription medications should be considered as ancillary to dietary or lifestyle modifications for chronic symptoms, but can be used during periods of acute symptom exacerbation.
3. *Psychological treatments.* Psychological treatments may be considered for motivated patients with moderate-to-severe GI symptoms and for patients with pain. It is more helpful if the patient can associate symptoms with stressors. These treatments, which include cognitive-behavioral therapy, relaxation, hypnosis, and combination treatments, help to reduce anxiety levels, encourage health-promoting behaviors, give the

patient greater responsibility and control regarding the treatment, and improve pain tolerance. See the article in this issue "Psychosocial Aspects of the Functional Gastrointestinal Disorders" on page 1447 in this issue for more details.

Severe symptoms. Only a small proportion of patients with FGIDs have severe and refractory symptoms. These patients also have a high frequency of associated psychosocial difficulties including diagnoses of anxiety, depression or somatization, personality disturbance, and chronically impaired daily functioning. There may be a history of major loss or abuse, poor social networks or coping skills, and "catastrophizing" behaviors. These patients may see gastroenterology consultants frequently and may hold unrealistic expectations to be "cured." They may deny a role for psychosocial factors in the illness and may be unresponsive to psychological treatment or to pharmacological agents directed at the gut.

1. *The physician's approach.* These patients need an ongoing relationship with a physician (gastroenterologist or primary care physician) who provides psychosocial support through repeated brief visits. In general, the physician should: (1) perform diagnostic and therapeutic measures based on objective findings rather than in response to patient demands, (2) set realistic treatment goals, such as improved quality of life rather than complete pain relief or cure, (3) shift the responsibility for treatment to the patient by giving therapeutic options, and (4) change the focus of care from treatment of disease to adjustment to chronic illness.
2. *Antidepressant treatment.* The tricyclic antidepressants (e.g., desipramine, amitriptyline), and more recently, the serotonin-noradrenergic reuptake inhibitors (e.g., duloxetine) have a role in controlling pain via central analgesia as well as relief of associated depressive symptoms. The selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine) may have an ancillary role as they are less effective for pain but can help reduce anxiety and associated depression. Antidepressants should be considered for patients with chronic pain and impaired daily functioning, coexistent symptoms of major or atypical depression, symptom anxiety, or panic attacks. Even without depressive symptoms, these agents may help when the pain is dominant and consuming. A poor clinical response may be due to insufficient dose or failure to adjust the dosage based on therapeutic response or side effects. Treatment should be instituted for at least 3 to 4 weeks. If effective, it can be continued for up to a year and then tapered.
3. *Pain treatment center referral.* Pain treatment centers provide a multidisciplinary team approach toward rehabilitation of patients who have become seriously disabled.

The Rome Committees and Criteria Development

Beginning about 15–20 years ago, and with greater recognition of the FGIDs, the academic environment was receptive to a classification system that could be used for research and clinical care. At this time, the Rome working teams began, and have since served as the nidus to modify and update information on these disorders. With no prior standards or evidence from research, the groups developed criteria by consensus (via the Delphi Approach).[99,100] Over time and with acquisition of new data, the process has matured through three generations, producing a series of publications (Rome I, II, and III), with an increased evidence-based approach to the recommendations. The Rome organization was incorporated in 1996 as the Working Teams for Diagnosis of Functional GI Disorders, became a 501(c)3 tax-exempt organization in 1997, and was renamed the Rome Foundation in 2003 to reflect the expansion of its activities globally. The Foundation continues its mission to improve knowledge of the science and practice relating to the functional GI disorders and has received support from academic organizations, investigators and clinicians, pharmaceutical regulatory agencies, pharmaceutical companies, and federal research agencies. See "The Road to Rome" on page 1552 in this issue for a historical account of the Rome Committee work.

Rationale for Symptom-Based Diagnostic Criteria

The Rome III classification system is based on the premise that for each disorder, there are symptom clusters that remain consistent across clinical and population groups. This type of organization provides a framework for identification of patients for research that are modified as new scientific data emerges. The rationale for classifying the functional GI disorders into symptom-based subgroups has several bases.[101]

Site-specific differences. Patients with functional GI disorders report a wide variety of symptoms affecting different regions of the GI tract. These symptoms have in common disturbances in sensory and/or motor GI function, or similarities in CNS processing of visceral and somatic signals. Despite overarching similarities in CNS functioning amenable to central treatments, many, if not most of the FGIDs have peripherally generated symptoms that require more specific treat-

ments (eg, for diarrhea or constipation). Furthermore, epidemiological studies using factor analysis and other methods provide the evidence for the existence of site-specific syndromes.[102–104]

Symptoms resulting from multiple influencing factors. Unlike motility criteria that define motor dysfunction, which can have varying or no symptoms (eg, gastroparesis, pseudo-obstruction, or "nutcracker esophagus"), symptom-based criteria are influenced not only by abnormal motility, but also visceral hypersensitivity and brain gut dysfunction. Therefore, each condition may have varying contributions from these pathophysiological determinants.

Epidemiologic data. Epidemiological studies show similar frequencies for these conditions across various studies and populations in Western countries including USA, Australia, England, and France,[105] but may be lower in Asian countries and in African Americans.[106,107] In addition, a factor analysis study using two community samples[108] identified an irritable bowel factor, and these symptoms were very similar to those developed from a clinical population of patients with IBS using discriminant function analysis ("Manning" criteria).[109] When differences do exist, these may relate to the type of criteria used, which may over- or underrepresent the population being tested.[110]

Treatment implications. A critical value to the use of symptom-based diagnostic criteria relates to the ability to define patient subsets amenable to treatment trials. Thus, centrally acting treatments can have overarching effects on pain in most all the FGIDs, whereas treatments for diarrhea or constipation can be targeted to appropriate subgroups using the specified criteria.

Need for diagnostic standards in clinical care and research. Because there are no unique physiological features that can characterize all the disorders, and because it is symptoms that patients bring to physicians, the use of a symptom-based classification system is rational for clinical care and research. Symptom-based criteria are used in psychiatry (eg, the Diagnostic and Statistical Manual of Mental Disorders-IV)[111] and rheumatology[112] and are becoming increasingly accepted within gastroenterology. Symptom-based criteria can help guide the diagnostic and treatment approach, reduce the ordering of unneeded diagnostic studies, and standardize patient selection for clinical trials.

Qualifications for the Use of Symptom-Based Criteria

There are several limitations and qualifications to the use of symptom-based criteria.[101]

Other diseases may coexist that need to be excluded. The high frequency of the FGIDs ensures their coexistence with other diseases. If 10%–15% of the population has IBS, then the same proportion with inflammatory bowel disease will also have IBS, and the evidence suggests that there is more than a chance association.[113] In fact, inflammatory bowel disease may even predispose to IBS.[114,115] Similarly, *Helicobacter pylori* needs to be excluded and/or treated among patients with functional dyspepsia. For research purposes, it is necessary to exclude other diseases before a functional GI designation can be applied. Therefore, for all criteria, the following statement holds: *there is no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms*. Physicians are well aware that in clinical situations, one must consider the presence of two or more conditions and make judgments on the proper treatments for both. One example would be a patient with IBS and inflammatory bowel disease having predominant pain and diarrhea not sufficiently explained by the morphological findings.

Symptoms may overlap with other functional GI disorders. It is common for functional GI disorders to coexist, and the criteria permit the coexistence of more than one FGID. Examples are esophageal chest pain (A2) or globus (A4), with IBS (C1) or fecal incontinence (F1). There are situations, however, in which a hierarchical classification of the FGIDs is required. For instance, when criteria for both IBS (C1) and epigastric pain syndrome (B1b) are fulfilled, the diagnosis of IBS only is made when the epigastric pain is relieved by defecation. Similarly, functional bloating (C2) exists only when IBS and the dyspeptic conditions are excluded, because bloating is common to both these other conditions, and a diagnosis of functional constipation (C3) is made only if IBS criteria are not met.

Symptoms must have begun 6 months prior to diagnosis and be active for 3 months. This time frame is a modification of the Rome II criteria and is less restrictive. Thus, onset of symptoms should begin at least 6 months before clinical presentation and the diagnostic criteria must be fulfilled for the last 3 months (rather than 1 year for Rome II).

Diagnostic categories do not include psychosocial criteria. Although psychosocial disturbances can affect the onset, course, severity, and outcome of the FGIDs, they are not required for diagnosis. Psychosocial disturbances are more common in patients seen in referral practices over primary care or in the community of nonconsulters.

Criteria are determined by clinical consensus and existing evidence. The proposed diagnostic criteria originated by the consensus of experts in the field and have since been modified only if there is compelling evidence to do so. All changes in criteria relate to a rationale that is provided in the chapter. In some cases, recommendations for changes (e.g., dyspeptic criteria, subtypes of IBS) are not yet proven but are supported by compelling evidence. New criteria will be tested in future studies now underway, which will form the basis for future modifications of the criteria.

The Rome Committee Process

The process for developing these criteria is a rigorous one. The consensus process was initiated by Professor Aldo Torsoli for the International Congress of Gastroenterology in Rome (Roma '88). Dr. Torsoli charged the committees[99] to use a "Delphi" method[100] of decision making, which fosters a team effort to produce consistency in opinion or consensus (although not necessarily total agreement) for difficult questions not easily addressed. The Rome II committees and more recently, the Rome III Board took on the responsibility to enhance these activities further using a rigorous 4-year, 13-step process outlined in the following points.

1. The Editorial Board identified individuals who fulfilled preset criteria (academic research record, name recognition, ability to work in groups, and diversity issues related to discipline, geographic location, and gender) to chair and co-chair each of the 14 subcommittees. The chair and co-chair were charged to coordinate their committee to develop a manuscript for the *GASTROENTEROLOGY* journal and a larger manuscript for the Rome III book.
2. The chair and co-chair, with consultation from the Board, recommended an international panel of up to five additional members fulfilling the same criteria previously noted to join the subcommittee.
3. The chair and co-chair designated each committee member to produce an initial document covering their particular area of expertise. The members are charged to critically synthesize the literature regarding the physiological, psychological, and diagnostic and treatment aspects of a particular functional disorder or scientific content area.
4. The chair and co-chair then incorporated all documents into a manuscript that was sent back to the entire committee for review (Document A).
5. This process of modification and re-review by the committee, repeated two more times (Documents B and C) over a 2-year period, is associated with critical appraisal and modification of the information presented by all members.
6. The committee met for two days in November/December 2004 to revise the documents. This face-to-face meeting led to consensus on the diagnostic criteria and scientific content.
7. The information was summarized and presented to the full committee of chairs and co-chairs over 1 day for feedback and harmonization of content across committees.
8. The chair and co-chair then revised the documents again (Document D) and sent them to up to six outside international experts, in addition to scientists in the pharmaceutical industry, for their review and commentary. This process was handled in collaboration with the Rome Foundation and the *GASTROENTEROLOGY* journal administrative staff.
9. Concurrently, the copy editor identified areas that required revisions relating to style and format and sent the changes to the chairs and co-chairs for modification.
10. The Editorial Board served as editors to facilitate and respond to the review process. Each Board member was responsible for two committees.
11. The committee chairs responded to the editor's and reviewers' comments either by modifying the manuscripts as requested, or by providing a written response that addressed the reviewer's concerns. In some cases, the manuscripts were reviewed and modified three times before final acceptance.
12. The revised manuscripts and the commentaries by the reviewers and authors were then sent to the Editorial Board who met in September and again in December 2005 to critically review these materials and submit any final comments back to the authors. In some cases, edits were made by the editors and were sent for approval to the committee chairs and co-chairs.
13. Finally, when the documents were completed, all members signed off their approval before it was sent to the copyeditor for a final check on content and style prior to publication.

Changes Made in Rome III

The changes from Rome II to Rome III reflect mainly updates in the literature and committee recommendations derived from these new data. In addition, a few modifications in the categories and criteria were made. The following information summarizes the changes, and the reader is referred to the relevant article for details.

1. *Time frame change for FGIDs*. Symptoms are now recommended to originate 6 months before diagnosis and be currently active (ie, meet criteria) for 3 months. This time frame is less restrictive when compared to Rome II (12 weeks of symptoms over 12 months) and is easier to understand and apply in research and clinical practice.
2. *Changes in classification categories*. Rumination syndrome moved from functional esophageal (category A) to functional gastroduodenal disorders (category B). This change reflects the evidence that this disorder originates from disturbances in the stomach and abdomen.
3. *Removal of FAPS from functional bowel disorders (category C) into its own category (category D)*. This revision is based on growing evidence that FAPS relates more to CNS amplification of normal regulatory visceral signals rather than functional abnormalities per se within the GI tract.
4. *Creation of two pediatric categories*. The Rome II category of Childhood Functional GI Disorders is now classified as Childhood Functional GI Disorders: Neonate/Toddler (category G) and Childhood Functional GI Disorders: Child/Adolescent (category H). This change is due to the different clinical conditions that arise between these two categories relating to growth and development of the child.
5. *Criteria changes*. For Rome III, functional dyspepsia (B1) is de-emphasized as an entity for research due to the heterogeneity of this symptom complex as defined. Instead, the committees recommend two conditions that are subsumed under the functional dyspepsia "umbrella": (1) postprandial distress syndrome (B1a) and (2) epigastric pain syndrome (B1b). These conditions are similar to dysmotility-like and ulcer-like dyspepsia of Rome II. They are now defined by a complex of symptom features with physiological support rather than being based on the previous requirement of epigastric discomfort or pain, respectively.
6. *More restrictive criteria for functional disorders of the gallbladder and sphincter of Oddi*. There are more defining features and exclusions required for symptom-based diagnosis of these conditions. In doing so, we have reduced the patient population that would then receive invasive studies such as endoscopic retrograde cholangiopancreatography and manometry to confirm the diagnosis and be treated.
7. *Revision of IBS subtyping*. The committees are recommending that diarrhea, constipation, and mixed subtypes should be based on a simple classification derived from stool consistency. The bowel subtyping used in Rome II for IBS-D and IBS-C is still acceptable, however.

We are hopeful that these changes will make the Rome III criteria more useful for research and clinical care. Future studies will be needed to confirm the validity of these changes.

Concluding Comments

It is with great anticipation that we introduce this issue of GASTROENTEROLOGY: Rome III, The Functional Gastrointestinal Disorders. We hope that the information will help the reader gain a better understanding of these disorders and help clinicians in the diagnosis and care of our patients. This work is the culmination of a 5-year effort of 87 internationally recognized investigators representing 18 countries. As we look back on the process, the information we have obtained is comprehensive, although certainly not complete. It is likely that the next 6 years will bring considerable advances in our understanding and treatment of these disorders, and when that occurs, we plan to revise the information as we move to Rome IV. As we look forward, we have taken on several new initiatives to continue our mission. These plans include new working team committees that have been instituted to develop standardization of brain imaging assessment and making recommendations relating to symptom severity for research and clinical care. We have also begun to capture this work and future scientific data into a CD slide set module for self-learning and lectures. Finally, we are looking to disseminate this knowledge through additional educational products on a global scale. The Rome process is a dynamic one, and we look forward to future activities to help improve the science of the FGIDs and patient care.

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