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VIEWPOINT

The 'Pro' case. The Rome III criteria

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INTRODUCTION

A recent editorial in the journal commented that: 'based on their prevalence and health-economic impact, disorders of gastrointestinal (GI) motor and sensory function continue to represent a major unmet need'.[1] Although all investigators working in this field would likely concur with the statement, it is important that we are clear in our minds what conditions these 'disorders' actually represent, and what nomenclature and classification we should use to describe and define them – in clinical practice, in research, and in discussions with regulatory and other authorities.

The term *functional GI disorders* (FGIDs) is used to define several variable combinations of chronic or recurrent GI symptoms that cannot be explained by structural or biochemical abnormalities.[2] In many instances, these disorders are likely to derive ultimately from a disturbance of gut function, be it motor, sensory or secretory. Moreover, because the FGIDs are defined by symptoms, they encompass many of the *primary motility disorders*, apart from those entities with documented histopathological lesions of the enteric nervous system (ENS) and/or central nervous system (CNS), such as achalasia or Hirschsprung's disease.

For most of the FGIDs, the nature and extent of objective GI tract motor and sensory dysfunction remains unclear.[3] It is also increasingly evident that some of the FGIDs have features in common, and overlap with, disorders in other systems such as fibromyalgia and interstitial cystitis; this suggests a more complex aetiology than once appreciated, involving brain-gut dysregulation associated with factors such as altered gut ecology, immune activation in the ENS, altered autonomic function, altered activation of CNS circuits and disorders of mood and affect.[4]

Over the previous 15 years, the Rome organization (now Rome Foundation) has worked towards achieving a better understanding and treatment of the FGIDs. One of its main activities has been the development of symptom-based criteria for the FGIDs. Given the continuing evolution and maturation of these 'Rome criteria' over the previous two generations of publications, and with the recent publication of the latest iteration – Rome III[5] – it is timely to reassess the current position and role of the criteria in the field. In addressing several issues relevant to Rome III, as suggested by the Editors, it will be evident that these criteria, because of the multi-factorial aetiology of the FGIDs, and despite the inherent limitations of symptom-based diagnostic criteria, remain an essential component of the research effort directed towards these disorders. It will also be evident that the criteria continue to have an important role in the clinical management of the FGIDs.

WHY IS ROME III AN IMPORTANT CONTRIBUTION TO THE BROAD AREA OF THE FUNCTIONAL GASTROINTESTINAL DISORDERS?

Before specifically addressing Rome III and its intended purpose, it is helpful to briefly review the contribution of the Rome process and the earlier publications to the field.

What the Rome process has already contributed

As detailed eloquently by Thompson,[6] the situation prior to the Rome process was that of very slow

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progress in understanding the FGIDs due to, among other factors, the multiple and idiosyncratic descriptions and definitions employed, and the overall lack of coherence in the literature. There can be little doubt that the energy, rigor and inclusiveness of the Rome process, as outlined by Dr Drossman in the preface, have met with widespread support from the academic community, and have been a huge impetus to the field. The Rome criteria are now regarded as an important 'anchor' to the field and have provided a necessary structure for the ever-increasing research activity in this area. The following are some of Rome's contributions – through its publications and other educational activities – to research, education and patient care,[7] and where any objective assessment of these contributions reveals the overall benefit to the field:

- Ability to provide a more positive diagnosis to patients. A diagnosis is the centre-point of a constructive doctor–patient relationship, and using the criteria, the physician can at least render a realistic explanation or meaning to the patient's symptoms.
- Substantial progress in legitimization of the FGIDs, leading to an enhanced awareness, understanding and appreciation of the socioeconomic importance of the disorders by clinicians, investigators and health regulators.
- Availability of specific criteria for research. The Rome criteria now form the basis for patient recruitment and entry into most research studies of FGIDs. This has been achieved through the comprehensive operational classification, the validated symptom questionnaires, and the recommended diagnostic criteria for the different disorders.
- Promulgation of specific guidelines for clinical trial methodology. The Rome principles of trial design are now 'industry standard' for drug and other therapeutic trials in the FGIDs.
- Impetus to basic and applied research in enteric neuroscience. The Rome criteria have provided a common 'language' for comparison of studies from around the world. They have also facilitated the increasing dialogue between organizations that share similar goals, such as the American Neurogastroenterology and Motility Society, European Society of Neurogastroenterology and Motility, Functional Brain Gut Research Group, the Motility and Nerve–Gut section of the American Gastroenterological Association, and the World Congresses of Gastroenterology, to move the field forward.
- Promotion of the biopsychosocial model to enhance clinical management of the FGIDs. This model takes into account that symptoms may be physiologically multi-determined and modifiable by sociocultural and psychosocial influences.

Why Rome III will achieve its intended purpose for clinicians and scientists

Rome III is the culmination of a 6-year effort to update the Rome criteria and to include the substantial amount of new information available on the FGIDs since Rome II; it provides a unique resource collating, synthesizing and placing in perspective the tremendous increase in research activity. The key elements of Rome II have been retained but, as Drossman[7] has noted, some of the practical aspects of patient classification have been made more 'user-friendly' for the clinic and for research.

Thus, for example, the time frame for the diagnosis of the FGIDs has been changed to be less restrictive when compared to Rome II, and easier to understand and apply. Symptoms should now have begun at least 6 months before clinical presentation and be currently active (i.e. meet criteria) for the last 3 months. Also, some criteria have been modified, particularly those for *functional dyspepsia* and *irritable bowel syndrome (IBS).* Although these revised criteria have not been validated, they are more strongly evidence-based. The entity of functional dyspepsia now acts only as an overarching term – but one that can still be used in clinical practice – for the heterogeneous group of symptoms that need to be considered. Two new specific categories of meal-induced dyspeptic symptoms (*postprandial distress syndrome)* and epigastric pain (*epigastric pain syndrome)* are defined, particularly for research purposes, based on evidence from epidemiological and physiological studies. For IBS, the new recommendation for subgrouping patients is based on a simple assessment of stool consistency, because this relates to intestinal transit. For the *functional gallbladder and sphincter of Oddi disorders*, more restrictive criteria are recommended that include a greater number of defining features and exclusions, to reduce the need for invasive procedures.

Other new features which should enhance the usefulness of Rome III for both clinicians and scientists are:

- A revised symptom questionnaire for epidemiological and clinical research, and for clinical practice, which now includes an estimation of threshold determinants, and which has undergone validation for some of the disorders.
- Inclusion of alarm signs or 'red flags' for use in clinical practice and research.

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- Inclusion of a brief set of items to help clinicians decide when to refer a patient to a mental health professional.
- New chapters on pharmacological and pharmacokinetic aspects of the FGIDs, and on gender, age, society and culture.
- Review of new research areas relevant to the field, e.g. brain imaging and CNS regulation of gut function, and mucosal immunology and inflammation, including postinfectious FGIDs.

WHY CONTINUE TO USE SYMPTOM-BASED CRITERIA FOR THE FGIDS?

Rationale for symptom-based criteria

One of the key features of the Rome III publication is the revision of the diagnostic symptom criteria for the FGIDs, based, as previously, on the expectation that disorders explained by histopathological lesions have been excluded. The original criteria were set up to duplicate the successful development of diagnostic classifications in psychiatry (DSM-III) and rheumatology (ARA criteria). As Tytgat[8] has stated, 'the premise is that for each symptom-based disorder, there are identifiable symptom clusters that emerge across clinical and population groups', and 'Rome III remains faithful to the basic principle of the process encapsulated in the premise that diagnosis, differential diagnosis and therapy of FGIDs might and should be facilitated by a precise symptom-based categorization of patient groups.'

A compelling reason for pursuing a symptom-based classification, of course, is that patients present to the doctor with a symptom or symptom complex, not a physiological dysfunction. In clinical practice, the criteria focus investigation and can prevent the need for costly and unnecessary studies. In research studies, the criteria have been successfully used to provide better patient homogeneity. To date, the Rome classification has stood the test of time and remains the most comprehensive and effective working classification available. There is epidemiological support for symptom clusters, based on factor analyses in defined symptom-based subgroups.[9] If this classification did not exist, another would certainly have been required to achieve further progress in the field.

Another reason for continuing to use a symptom-based classification is that, despite years of study, as yet no common or disorder-specific physiological (or other) biomarker has emerged to enable alternative diagnostic criteria for these disorders: until such biomarkers are available, the symptom criteria represent useful patient descriptors for further study. Indeed, as further data appears, it is clear that certain FGIDs are characterized by a number of diverse pathophysiological factors acting in concert, and are not dependent on a single mechanism or factor that can be used for an objective diagnosis and for treatment response. For example in postinfectious IBS, several factors, such as infection and psychological distress, appear to be required to occur together in a subject to produce the syndrome. Far from negating the usefulness of a standardized symptom profile, this scenario virtually mandates its use. On the other hand, in examining a different FGID, if a single mechanism is operative in patients with that disorder, or if discrete and independent mechanisms exist within patients with that disorder, such mechanisms should remain definable in properly designed psychophysiological research studies.

Why the current number of FGID is appropriate

Given the current necessity for a symptom-based classification of the FGIDs, it is reasonable to ask whether the revised structure is appropriate. The Rome III classification includes 28 adult and 17 paediatric FGIDs.[5] Although on first encounter this may appear to be a relatively large and perhaps over-ambitious segmentation of symptoms/symptom complexes, it must be remembered that in the adult group there are six major domains included; these correspond to the five separate anatomical regions of the gut that require consideration, plus the category of *chronic abdominal pain syndrome*.

Within each gut region there are then several symptom groups, each of which appears to have relatively specific clinical features. Depending on the region, some disorders focus on a single symptom, while others consider clusters of symptoms. It seems logical, although not proven, that such a careful evaluation of the presenting symptoms may lead to a more fruitful exploration of the pathophysiologies. Thus, although some symptoms (e.g. diarrhoea, constipation, bloating and pain) may overlap across these disorders, IBS, for example, is specifically defined as pain associated with a change in bowel habit, and is distinct from *functional diarrhoea*, categorized by loose stools and no pain, and from *functional bloating* where there is no change in bowel habit. Each condition also has some differences in diagnostic and treatment approaches. For example, in the case of the three main oesophageal disorders, namely *functional heartburn, functional chest pain of presumed oesophageal origin,* and *functional dysphagia*, these catego-

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ries are relevant not only to identify more homogeneous patient groups for study, but also to facilitate the appropriate exclusion of the various forms of structural disease that can present with similar symptoms.

Some of the disorders are very well-established, such as IBS, the first to be described, while others require much more evaluation either to achieve greater legitimacy or to be shown to require modification. It is likely, in fact, that the current classification will need extensive revision with the accumulation of more knowledge. One could argue that a different symptom classification system may be more useful, but to date no such alternative system is available. Some other approaches are being explored, e.g. subgrouping of IBS patients based on the principles of Traditional Chinese Medicine,[10] but these types of approaches seem unlikely to gain general acceptance. The current classification is certainly preferable to the previous *ad hoc* situation, or to the use of unhelpful terms such as 'gas-related symptoms'.

Limitations of symptom-based criteria

All committee members who contributed to the development of the Rome III criteria would recognize that these are by necessity imperfect, and represent work in progress. Hence, they remain open to well-founded criticism. A continuing criticism is that the criteria were originally devised largely by consensus, due to the lack of available data for most of the disorders. Consensus criteria, of course, do not represent evidence-based criteria, and this situation remains largely unchanged. Many of the criteria do not include a physiological alteration or other dysfunction, as this remains not feasible in our current state of knowledge. However, there are several important exceptions, and the Rome III criteria for the *functional defecation disorders*, for example, incorporate recent evidence from manometric and imaging studies suggesting that inadequate propulsive forces may be a cause of these disorders.[11]

Some of the criteria changes for Rome III also require validation as discussed earlier; this is especially true for the category of functional dyspepsia. This category certainly has proven to be one of the most difficult and controversial areas since the Rome process began. It is clear that no single symptom is present in all patients and that there is considerable variation in the overlap of pain and discomfort. The Rome III committee thus has defined functional dyspepsia as the presence of one or more dyspeptic symptoms that are considered to originate from the gastroduodenal region, in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms. The specific symptoms are postprandial fullness, early satiation, and epigastric pain or epigastric burning, and these symptoms are clearly defined in the relevant chapter. For experimental purposes however, the committee recommended replacing the term functional dyspepsia by the two more distinctively defined disorders, postprandial distress syndrome and epigastric pain syndrome.[12] The rationale for this new proposal is based on the inadequacy of previous approaches such as the predominant symptom, as well as the results of recent factor analyses. As discussed in detail,[12] consistent symptom groupings in the literature include an epigastric pain factor, a factor of meal-induced symptoms including postprandial fullness or early satiation, and a nausea factor (with or without vomiting). These groupings form the basis for the classification of the *functional gastroduodenal disorders*. Encouragingly, the entity of postprandial distress syndrome has recently been shown, albeit in a preliminary retrospective study, to be associated with a higher prevalence of impaired accommodation to a meal, while gastric hypersensitivity appears more prevalent when subjects suffer from both postprandial distress syndrome and epigastric pain syndrome.[13]

Another criticism of the criteria is that they are too detailed and time consuming to employ in clinical practice and it is true that to date uptake of the criteria by clinicians has been slow. Certainly, the criteria could be presented in a more clinically relevant format than undertaken so far, and clinical diagnostic algorithms are planned for this purpose. However, particularly in regard to gastroenterologists, the prominence afforded endoscopic procedures, perhaps at the expense of comprehensive history-taking, may also be a factor. This is not an inconsequential situation, as appropriate use of the criteria would very probably reduce the endoscopic load.

A further criticism raised is the apparent overlap of symptoms in several FGIDs. However, when a symptom is common to two or more disorders, the classification is designed to be necessarily hierarchical. For example, functional bloating is diagnosed only when IBS and dyspeptic conditions are excluded, as bloating can occur in both these other conditions.[7] This is reasonable, given that the pathogenetic mechanism of bloating may well differ according to the presence or absence of an altered bowel habit, or the presence or absence of dyspeptic symptoms. Similarly, *functional constipation* is only diagnosed if IBS criteria are not met.[7] If an investigator wishes to carry out pathophysiological studies focused on a particular symptom, it is of course quite feasible to

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study and compare two or more Rome disorders with a common symptom in the one protocol, e.g. IBS with bloating and functional bloating. Finally, the issue of severity of the FGIDs is an important and difficult area not adequately addressed by the current criteria. This aspect is currently being considered by a Rome working party.

ARE THERE ADDITIONAL CRITERIA THAT SHOULD BE CONSIDERED TO ENHANCE SYMPTOM-BASED CRITERIA?

Given the limitations of the symptom-based classification, it is reasonable to consider other or additional forms of classification. Ideally, each of the symptom-based disorders would be accompanied by a physiological or other correlate or correlates; unfortunately this is the case with only some of the FGIDs, in particular the functional defecation disorders and the functional gallbladder and sphincter of Oddi disorders, and to a lesser extent the functional oesophageal disorders.

There has been a surprising lack of emphasis in the literature on re-evaluating the classification of the GI motility disorders; this is important given the prominence of visceral hypersensitivity and other related phenomena. The classification of the GI motility disorders thus remains based on regions of the GI tract, as with the FGIDs, or – less useful clinically – based on neuropathology of the central and peripheral nervous systems.[14] The former classification depends on the demonstration of a physiological (motor) dysfunction, often of specific gut regions, on relatively straightforward manometric or scintigraphic techniques, in particular disordered GI transit such as delayed gastric emptying and slow colonic transit; unfortunately, the reproducibility of these dysfunctions is in some cases less than ideal. A further confounding factor is that patients with these alterations may have varying symptoms or even no associated symptoms at all!

Although the phenomenon of visceral hypersensitivity appears to be one of the more reproducible dysfunctions in the FGIDs, despite early promise, it cannot be regarded as a biomarker as measured by currently available techniques, and it has not yet reached the clinical arena. There is some evidence, however, that it may be organ-specific (i.e. gastric or rectal) in patients exhibiting a specific FGID, namely functional dyspepsia or IBS;[15] this type of data supports the use of the site-specific symptom-based categorization. Attempts to identify other pathophysiology-based subgroups in functional dyspepsia have not met with great success, as there is considerable overlap between different abnormalities within the dyspeptic symptom population.

Other potential biomarkers in the FGIDs include mucosal histology, cardiovascular reactivity, gut permeability and blood, stool and genetic markers. Unfortunately, none of these of have as yet proved reliable or accurate enough to supplant, or form part of, the symptom-based criteria.

CONCLUSION

The Rome III process has again attracted the interest and participation of many in several disciplines from around the world. Just as the physiological and psychosocial research strands in the FGIDs remain at times contradictory and fragmentary, so the symptom criteria and overall Rome classification represent work in evolution. Although they are regarded by all concerned as being imperfect, it can be concluded that their advantages outweigh their disadvantages, and the key point is the facility for their ongoing refinement and reassessment periodically (every 6 years to date) according to evolving evidence. As Thompson[6] has stated, Rome III is 'only the continuation of an ongoing process that will last as long as the pathophysiology of FGIDs eludes us'.

So, with a symptom-based framework remaining firmly in place, it is in the hands of investigators in an expanding range of disciplines to continue to work towards identifying potential biomarkers and pathophysiologies for the FGIDs, and to determine if distinct patient groupings can be identified on this basis to facilitate new therapies.[16,17] It is also up to clinicians to embrace the symptom-based classification and to evaluate further its utility in clinical practice. At the very least, in so doing, more attention will be paid to the nature and impact of a patient's presenting symptoms, a more definitive diagnosis provided to the patient, and a more positive patient–doctor relationship established.

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