The Road to Rome

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The traditional medical diagnosis of disease requires observed anatomical or physiological abnormalities. Description of the disease's symptoms and signs follows naturally. Clinicians can then predict the anatomic diagnosis by recognizing these symptoms and signs in their patients. In the case of the functional disorders, such a process is impossible. Since there are no observed pathophysiological defects, we only know of the existence of the disorders through the words of our patients. The movement to define these disorders of unknown pathology represents a substantial change in thinking for doctors whose training concentrates on basic science and palpable "evidence." Since more than half of gut disorders encountered by gastroenterologists and primary care doctors are functional, we must face the reality that no current scientific evidence explains these disorders, and develop alternate methods to identify them.

For too long, functional diseases were described by what they are not, rather than as real entities. Yet they are real enough to patients. Not only does such an exclusive approach fail to provide the patient with the dignity of a diagnosis, but it also generates needless tests and consultations. The fruitless pursuit of an anatomical cause renders functional disorders "diagnoses of exclusion." Their very numbers and cost demand a more positive approach.

More seriously, there was a disconnect between the subjects chosen for randomized clinical trials (RCTs) and the labels used in clinical practice. Because clinical scientists failed to describe their subjects accurately, the results of their RCTs are of uncertain applicability to the patients encountered by practicing doctors. In a 1988 critique of 43 clinical trials of irritable bowel syndrome (IBS) treatments, Klein[1] observed that 58% of them reported "absolutely nothing about the criteria by which IBS patients were selected." There were important differences among the remainder, some not requiring abdominal pain, and others not even requiring a bowel habit abnormality. Klein concludes, "Not a single IBS treatment trial reported to date [1988], used an adequate operational definition of IBS."

Table 1 further illustrates this point. Many of these reports were published in prestigious journals and in some cases form the basis of regulatory approval of drugs that remain on national formularies. Most of these reports implied that the diagnosis of their subjects rested solely on the exclusion of structural disease. The trials shown in Table 1 include IBS or irritable colon syndrome (ICS) in their titles, yet they describe very different trial subjects. The listed trimebutine trials were the basis of regulatory approval in France, Canada, and elsewhere, yet the entered patients in these "IBS trials" were dissimilar. The trial reports in Table 1 fail to state entry criteria that would permit doctors to judge which patients should receive the tested treatments. This lack of definition was similar for dyspepsia and constipation. It was time to define and establish criteria for the functional gastrointestinal disorders.

There are many references to gut dysfunction in the ancient and early European literature. However, the first credible English language descriptions of irritable bowel syndrome (IBS) appeared in the early nineteenth century. One such description of the IBS in 1818[2] drew attention to three cardinal symptoms of IBS: abdominal pain, "derangement of... digestion," and "flatulence." A few years later, Howship[3] described a "spasmodic stricture" of the colon reflecting the enduring, but unsubstantiated belief that functional gut disorders are somehow the product of gut spasm. Mid-century brought more sophisticated treatises (and very unsophisticated cures such as purging and "electrogalvanism"). In 1849, Cumming[4] exclaims incredulously, "the bowels are at one time constipated and at another lax in the same person ... how the disease has two such different symptoms I do not propose to explain." Were he to return to a modern IBS consensus meeting, he would discover that this enigma remains! Cumming's treatise contained one other comment in line with modern thinking about IBS. "One can tell, without more minute examination what the nature of the complaint is." The authors of this book agree with Cumming's notion of a positive diagnosis, even though many doctors persist in recognizing IBS and the other func-

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Table 1. Irritable Bowel Syndrome Entry Criteria for Randomized, Controlled Trials Prior to 1988

Author	Year	Journal	Drug	Entry criteria
Kasich[24]	1959	AJ Gastro	*tricyclanol*	irritable colon syndrome (ICS)
Connell[25]	1965	BMJ	*mebeverine*	ICS
Tasmen-Jones[26]	1973	N Z J Med	*mebeverine*	abdominal pain & altered bowel habit
Greenbaum[27]	1973	NEJM	*diphenylhydrate*	compatible history of irritable bowel syndrome (IBS)
Piai[28]	1979	Gastroenterology	*profinium*	compatible history of IBS
Moshal[29]	1979	J Int Med Res	*trimebutine*	constipation—10% had pain
Fielding[30]	1980	Irish Med J	*trimebutine*	diagnosed as suffering from IBS
Luttecke[31]	1980	Curr Med Res Opin	*trimebutine*	IBS on the basis of their symptoms
Fielding[32]	1981	Digestion	*timolol*	IBS
Cann[33]	1983	Gut	*domperidone*	abdominal pain and bowel disturbance suggestive of IBS
Dew[34]	1984	Br J Clin Pract	*peppermint oil*	typical symptoms of IBS
Flexinos[35]	1985	Eur J Clin Pharm	*trimebutine*	constipation or diarrhea or both
Pidgeon[36]	1985	Ir J Med Sci	*cimetidine*	IBS patients with excessive muscle spasm on sigmoidoscopy
Narducci[37]	1985	Am J Gastro	*nifedipine*	abdominal pain relieved by defecation and either constipation or diarrhea
Perez-Mateo[38]	1986	Int J Clin Pharm Res	*Diltiazam*	compatible clinical history, physical exploration
Prior[39]	1988	Aliment Pharm Ther	*lidamadine*	abdominal pain and distress with abnormal bowel habit
Dobrilla[40]	1990	Gut	*cimetropium*	abdominal pain "after all other organic causes . . . excluded"

NOTE. Data for 2005 were collected on January 31, 2006 and are therefore incomplete.

tional gut disorders only after the patient has undergone exhaustive investigation.

Medicine's understanding of IBS progressed little during the next 120 years. Indeed, it may have lost ground! Edwardian physicians considered functional disorders to be diseases of the wealthy. In fact, only the affluent could afford to be the patients of those Harley Street doctors who published their observations in the medical literature.[5] Constipation became associated with uncleanness.[6] The notion of "autointoxication" due to retained colon contents prompted an urge to purge that persists to this day. In the 1920s and 1930s, pejorative descriptors such as "psychogenic," "neurogenic," and "The Abdominal Woman"[7] did little to help patients with functional gut disorders. Proctalgia fugax was long thought to be a disease of young professional males, because only doctors had the temerity to describe their symptoms in letters to the editor of the *Lancet*.[8] Use of terms such as "spastic colitis" and "hyperacidity" inferred now-discredited etiologies for these disorders.[6]

The first systematic attempt to bring discipline to this area was a 1962 retrospective review of IBS patients at Oxford by Chaudhary and Truelove.[9] The authors reported symptoms that we recognize to be those of IBS (or ICS as they termed it). They even separated IBS from what we now call functional diarrhea, and noted that one quarter of their patients' complaints began with an enteric infection. Their report ushered a new era, and scientific publications on functional disorders increased rapidly thereafter (Figure 1).

The table of contents of my book *The Irritable Gut* (1979) contained the first classification of the functional gastrointestinal disorders.[10] In 1978, Ken Heaton et al reported results obtained by questionnaire administered to Bristol outpatients with abdominal pain and disordered bowel habit.[11] The 6 of 15 symptoms we found more common in IBS than organic gut disease (diagnosis determined by a chart review a year later) became the *Manning Criteria*. In 1984, Kruis et al from Germany reported a similar study.[12] Their report recalls the 3 cardinal IBS symptoms of pain, bowel dysfunction, and flatulence mentioned by Powell in 1818. If all 3 were present, IBS was highly likely. Kruis et al stressed chronicity and other symptoms as well, but their major contribution was to record "alarm" symptoms that should alert the physician to organic disease. These two

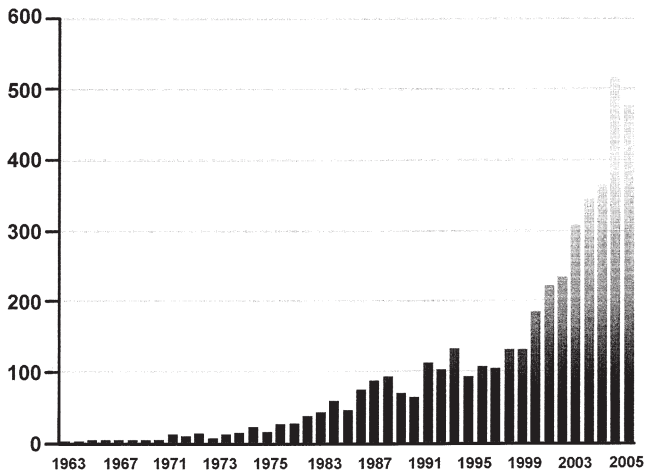

Figure 1. Annual results of PubMed literature searches for irritable bowel syndrome (IBS) and irritable colon syndrome (ICS) between the 1962 Chaudhary and Truelove report and December 2005. Note the rapid rise in publications during that period. While half the publications in the 1960s had ICS in their titles, only 1 or 2 do so now–exclusively in the non-English literature.

Table 2. History of the Rome Diagnostic Criteria

The Manning Criteria for IBS (1978)[11]
The Kruis Criteria for IBS (1984)[12]
The Rome Guidelines for IBS (1989)[15] (*Rome-2 IBS Criteria*)
The Rome Classification System for FGIDs (1990)[16] (*Rome-1*)
The Rome I Criteria for IBS (1992)[20] and the FGIDs (1994)[22]
The Rome II Criteria for IBS (1999)[41] and the FGIDs (1999)[23]
The Rome III Criteria (2006)

discriminate function studies in addition to epidemiologic data provided by Drossman[13] and Whitehead[14] are the basis of the Rome criteria for IBS.

The inspiration for the Rome process was an IBS symposium at the 12th International Congress of Gastroenterology held in Lisbon in 1984. Despite being perhaps the earliest international symposium on IBS, the symposium attracted an audience that far outstripped the capacity of the assigned room. One panel member, Professor Aldo Torsoli, was an organizer of the next international congress planned for Rome in 1988. Over coffee in Portugal, we discussed the need for guidelines for the management and study of IBS. A working team was set up to produce such guidelines for the next congress.

As chair, I collaborated with Doug Drossman (USA), Ken Heaton (UK), Gerhard Dotteval (Sweden), and Wolfgang Kruis (Germany) for 2 years. In 1987, we met in Rome to debate a draft proposal and reach consensus. We sent the penultimate draft to 16 expert colleagues in 7 countries. The working team considered their comments and suggestions and presented the first Rome criteria at the 13th Congress in Rome in 1988. The guidelines were published the following year.[15] Guidelines were this report's objectives, and diagnostic criteria were subordinate. They might be known as the *Rome-2 IBS Criteria*, and attracted much interest among researchers and pharmaceutical companies (Table 2).

Following that Rome meeting, Professor Torsoli and Dr. Enrico Corrazziari invited Dr. Doug Drossman to set up another committee to consider subgroups of IBS. After discussion, the project expanded to include all the functional gastrointestinal disorders. This working team, which included most of the this book's editors, met in Rome to classify the functional gastrointestinal disorders into 21 entities in 5 anatomical regions of the gut.[16] This was the first time that diagnostic criteria were proposed for all the functional gut disorders and included the first revision of the 1988 IBS criteria and could be considered *Rome-1*.

With sponsorship organized by Professor Torsoli, Doug Drossman organized a succession of working teams over 4 years that further developed these criteria in the 5 anatomical regions (esophageal,[17] gastroduodenal,[18] biliary,[19] bowel,[20] and anorectal[21]) and discussed topics related to functional gut disorders. In 1994, their collective work was updated and published in *The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment; a multinational consensus*.[22]

While this work is now known as *Rome I*, it includes the third rendition of the Rome IBS criteria.[20] From 1988 to 1992, three IBS working teams added duration parameters, and pain went from being unnecessary for the diagnosis of IBS,[15] to being a suggested symptom,[16] to eventually a requisite.[20]

The *Rome II* process included 4 years of deliberations by over 50 investigators from 13 Western countries organized into 10 committees. The result was the second edition of *Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment; a multinational consensus*. This iteration encompassed several important innovations. George Degnon became the Rome organization's executive director in 1994 and provided logistic and management support for a greatly expanded process generously funded by several pharmaceutical companies. Carlar Blackman became the administrative coordinator for the Coordinating Committee and the working teams. The organization became separated into an operational component (fundraising, meeting planning, book publishing) managed by Degnon Associates, and an academic component coordinated by Ms. Blackman and the Coordinating Committee. To ensure that the Rome process remained at arm's length from the sponsors, the Industry Research Council (IRC) was created with Dr. Bill Whitehead as chair. The IRC meets annually to allow Rome committee members, representatives of the sponsoring companies, and regulatory authorities to discuss progress and mutual concerns. Working team members do not communicate directly with the sponsors, and participating individuals must report their industry relationships. Rather than meeting independently, the working teams met together in Rome in 1998. This permitted interaction and harmonization among the committees. The Rome II criteria and essential supporting information were published in a *Gut* supplement in 1999.[23] In addition to the anatomically determined criteria and clinical trials working teams, new teams addressed basic science, neurogastroenterology, psychosocial issues, and pediatric functional gut disorders. The second edition of the book, also published in 1999, included a glossary, proposed questionnaires, and the results of a Vienna symposium on the *Definition of a Responder* involving academics, regulators, and the pharmaceutical industry.

By 2000, there was great interest in the Rome process as more researchers and interest groups entered the field, and the pharmaceutical companies and regulators became concerned how to define and test treatments for the functional gastrointestinal disorders. Thus, plans for *Rome III* began promptly. Dr. Robin Spiller and Dr. Michel Delvaux joined the now 7-member Coordinating Committee. The organization registered as a non-profit educational foundation, and the Coordinating Committee became known as the *Rome Board*. The Board held a retreat in London in February 2002 to plan its future. The Board agreed upon a Rome III format and addressed a wide range of operational topics including relationships with industry; projects such as validation that went beyond publication of diagnostic criteria; the promotion of evidence as the basis of criteria change; and the encouragement of "developing world" participation. The Board also initiated an ongoing project to develop an educational slide program for the functional gastrointestinal disorders.

For Rome III, the Board selected 87 participants from 18 countries in 14 committees and briefed the chairpersons in 2003, 2004, and 2005. Members were added from developing countries including China, Brazil, Chile, Venezuela, Hungary, and Romania. New working teams were created for gender, society, patient, and social issues; and pharmacology and pharmacokinetics. Functional abdominal pain was split from functional bowel disease and 2 committees (neonate/toddler and child/adolescent), rather than 1, served pediatrics. A subcommittee of the board consisting of myself (chair), Doug Drossman, Nick Talley, Lynn Walker, and William Whitehead designed the adult and pediatric questionnaires as the criteria were developed. Rome III culminated in a meeting in Rome in November/December 2004. As the final drafts of the chapters were being prepared, Dr. Whitehead conducted a validation study of the criteria and the questionnaire designed by the questionnaire subcommittee, the results of which are included in this publication. Following peer review, the results of the process are now published as articles in GASTROENTEROLOGY, and in full as the third edition of *Rome III, The Functional Gastrointestinal Disorders* in the summer of 2006. In addition, Board members reported the Rome III process to the 2005 World Congress of Gastroenterology in Montreal, and the criteria themselves to the 2006 American Gastrointestinal Association meeting in Los Angeles.

The Rome criteria generate much energy and controversy. They are imperfect. Validation studies are difficult and rare. There is much debate within the Rome processes about terminology, notably the use of the term *functional.* How much physiological or structural evidence is necessary for an entity to cease being functional? How long, how often, and how severe must symptoms become before they constitute a functional gastrointestinal disorder? Tradition and the lack of viable alternatives make change difficult. Those interested in the functional disorders express disparate views on these and other issues—epidemiologists, primary care physicians, consultants, researchers, psychologists, physiologists, pharmaceuticals, regulators, third party payers and, of course, the patients themselves. In Rome III, these voices were prominent in the background and in the reviews of the chapter manuscripts.

Despite the controversies, the criteria have gained such currency that they are the basis for entry into most research studies of functional gut disorders and have compelled an accurate description of entered patients in the remainder. They are the industry standard for entry into clinical drug trials, although they are sometimes modified to suit the characteristics of the product to be tested. They have given these disorders, particularly IBS, a profile. Patients can now be reassured they suffer from a legitimate disorder, not symptoms rendered imaginary by a negative test. The criteria have created a language with which the above-mentioned groups can communicate. The coming together of such disparate constituencies in a common effort is a major achievement, due in no small way to Rome's systematic recognition of the functional gut disorders.

This Rome III publication culminates a new 6-year effort to update the Rome criteria and, like Rome I and II, owes much to the energy and drive of Doug Drossman who describes the mechanics of this process in Chapter 1. The Rome II and Rome III processes were generously supported by industry, and attracted the interest and participation of many people in several disciplines from around the world. There can be no better testimony to the stature that the Rome criteria have achieved. However, Rome III is neither the end, nor even the beginning of the end. It is perhaps the end of the beginning of an ongoing process that will last as long as understanding the pathophysiology of functional gut disorders eludes us. Meanwhile, here is a great need to generate data that will sharpen the criteria and validate their use. Preliminary discussions have begun for *Rome IV*, but we must allow sufficient time for the accumulation of evidence to justify meaningful changes. The Delphi approach may be less useful now, but the need remains for consensus as to the meaning of the slowly accumulating, fragmented, and controversial evidence.

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