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VIEWPOINT

The 'Con' case. The Rome Process and Functional Gastrointestinal Disorders: the barbarians are at the gate!

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THE GLORY THAT WAS ROME

> *Marmoream se relinquere, quam latericiam accepisset. Tutam vero, quantum provideri humana ratione potuit, etiam in posterum praestitit*
> ('He found Rome a city of bricks and left it a city of marble. He made it safe too for the future as far as human foresight would provide for this'. Suetonius ca AD 69/75-130, The Lives of the Twelve Caesars, Book II, Augustus.)

In his preface to the first edition of the 'Functional Gastrointestinal Disorders', Douglas Drossman outlined the goals of the process that we have all come to know and love as 'the Rome criteria' to:[1]

1 make a positive diagnosis of these disorders,
2 understand their pathophysiology and
3 make effective treatment choices.

Clinicians and clinical investigators inundated with patients for whom the only diagnostic path was one of exclusion (and mutual exhaustion) and frustrated in their attempts to compare each others clinical observations and to design therapeutic trials, flocked to Rome where the deliberations and conclusions of the cognoscenti could be received and a new way forward revealed. The functional gastrointestinal disorders (FGIDs) previously vague, often dismissed and, at times, even ridiculed by the more 'organic' among the medical fraternity achieved, through the seal and protection of mighty Rome, a legitimacy and credibility which their advocates had long yearned for. These disorders could be crisply defined and delineated from each other; subsequent studies revealed the promise of Rome. Through the application of its criteria it became clear that these disorders were very common, were of far greater impact to those who suffered from them and their economic and social import was considerable. Very soon the world recognized that a mighty empire had emerged in their midst and that it would come to rule this vast territory for decades to come. Governments, through their regulatory agencies, acknowledged the emergence of Rome and the giants and minnows of the pharmaceutical industry stood up and recognized that, through Rome, vast riches were within sight: patient populations for clinical trials could be neatly defined, subpopulations characterized and responsive end points developed. Investigators envisaged a time when, by applying the doctrines of Rome, the pathophysiology of the various FGIDs and their subtypes would reveal themselves before their very eyes. Even the lowly clinician could now look forward to a day when he, or she, could dispense with expensive and invasive tests, look the patient in the eye and confidently deliver a 'positive' diagnosis, because Rome had so ordained. All basked in the glory that was Rome!

EXTENDING THE BOUNDARIES OF EMPIRE

Rome began its days as a small village in central Italy and slowly, but surely, expanded to govern the plain of Latium, later extending its rule to Etruria and, ultimately, to the entire mainland of modern Italy. Prolonged, costly Punic wars led to the fall of Carthage and the extension of Roman influence to Sicily and North Africa; subsequent campaigns resulted in the extension of the Roman realm to the Iberian Peninsula,

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Gaul, Macedonia, Syria and Egypt. Such was the ultimate extent of the empire that it became necessary to establish two capitals to govern a domain which now extended from the Atlantic to Asia and from Hadrian's Wall to the Sahara; such a vast territory exposed vulnerabilities and was, ultimately, unable to sustain attack on multiple fronts.

The Rome process had similar, humble origins; seeking to address 'the need for guidelines for the management and study of irritable bowel syndrome (IBS)'. By the time, the process was formally 'Romanized' the task had been expanded to encompass 'functional disorders of the oesophagus, gastroduodenal, bowel, biliary and anorectal regions';[2] Rome III now presents a grand total of 28 adult and 17 paediatric FGIDs![3] Has it too overextended its reach?

While some of these disorders, such as Globus, Cyclic Vomiting Syndrome, Rumination Syndrome and Proctalgia Fugax, pre-dated Rome and were long recognized as discrete entities, others, such as the Functional varieties of Heartburn, Chest Pain, Dyspepsia, Bloating, Diarrhoea and Constipation have emerged and been refined by the Rome process.

It is now 20 years since the first 'Rome' meeting; has this process advanced the goals it set out to achieve? It is this author's estimation that Rome can boast two major victories.

1 Generating overdue interest in the functional disorders.

2 Making considerable progress in the codification of IBS.

These have, however, been pyrrhic victories marred by a failure to resist the temptation to over-reach and 'define' every complaint potentially referable to the gastrointestinal tract. The risks of this strategy are best exemplified by 'functional dyspepsia'; the fact that Rome III sees a complete re-definition of this elusive entity speaks volumes for the integrity of this very concept. The intervening years between Rome's I and III have witnessed a plethora of confusing and contradictory data on the pathophysiology of FD and no progress in therapy. Given the difficulties intrinsic to the transcultural interpretation of 'dyspeptic' symptoms, confusion persists on the definition of the very symptoms which are used to define this disorder.[4,5] Furthermore, the extent of overlap between FD, IBS and gastro-oesophageal reflux disease (GORD), and shared aetiological features between these entities, beg a very fundamental question: does FD even exist? It is interesting to note that, in Asia, 'upper' symptoms feature prominently in the definition of what is regarded as IBS;[6,7] is Western FD no more than IBS with an emphasis on complaints which apparently originate from the foregut? In this apparently common 'syndrome', Rome has failed in each of its original goals: the diagnosis of FD has not been facilitated, its pathophysiology remains as disputed as ever and no new therapies have emerged.

Is there really a need to make a syndrome out of every symptom, for example, is there really any evidence that 'functional bloating' exists as a discrete entity? Are many of these supposedly discrete entities not merely part of a single continuum? Similarities in demographics, comorbidities, pathophysiology (visceral hypersensitivity, dysmotility and abnormal cerebral perception being ubiquitous) and precipitating factors (stress, psychological distress and food ingestion) suggest more commonality than differentiation. Indeed, the divisions of Rome have not revealed new insights into the fundamental causes of these symptoms; progress in IBS can readily be extrapolated onto any of these supposedly separate entities.

This expansion has not served Rome well, credibility gained in progressing our understanding of IBS has been tarnished by attempts to create new entities and, ultimately, therapeutic targets, where scanty evidence exists to support such creations. Some of these far-flung provinces of the Rome process have proven distinctly treacherous; the popularization of functional gallbladder and biliary disorders has undoubtedly led to many an unnecessary cholecystectomy and potentially hazardous endoscopic retrograde cholangio-pancreatographic (ERCP) examination, an outcome recognized in Rome III by the application of more restrictive definitions to these areas.[3]

DIVIDE AND CONFUSE

Gallia est omnis divisa in partes tres ('Gaul is divided into three parts'. Caesar, The Gallic Wars).

To Caesar, the division of Gaul represented a challenge to be overcome; the Rome process, in contrast has sought to develop subdivisions within entities whose very own existence, in some cases, is in doubt. Caesar subjugated the Helvetii, Suebi and Arverni, among others, ultimately defeating Vercingeterix and uniting the entire area under the standard of Rome. Rome's I to III, in contrast, have attempted to subtype FD and IBS, (each also *in partes tres*) the former now discarded, and the latter reworked. The subtyping foray into FD served merely to further emphasize the frailty of the very concept of FD, 'reflux-like dyspepsia' ultimately retreating into the mists of GORD while 'motility-like dyspepsia' defected to IBS. Sorties into IBS have been no less

traumatic; here the '*partes tres*', constipation-predominant, diarrhoea-predominant and alternating IBS being seen to be unstable and, indeed, interchangeable over time and not necessarily reflective of differences in underlying pathophysiology.[8,9] Furthermore, a failure to recognize that, in the strictest terms (stool weight), most, if not all, IBS patients do not have either diarrhoea or constipation but rather variable difficulties and concerns regarding bowel action which are expressed and willingly and unwittingly interpreted as such by the unwary doctor, has had some serious consequences. Encouraged by the prospect that some IBS patients can be categorized into groups which would be predicted to respond to either prokinetic (and thus laxating) or motility-inhibiting (and thus antidiarrhoeal) agents, pharmaceutical companies have gone on to develop IBS therapies tailored to the appropriate subtype. Not surprisingly, given that IBS patients do not have true diarrhoea or constipation, in the first instance, and that subtypes change over time, these approaches were troubled by significant adverse event issues related to the occurrence of either constipation or diarrhoea. Here, the Rome process has been no wiser than the hapless emperor Valens who, adhering determinedly to woefully inaccurate intelligence, led his legions into the battle of Hadrianople only to be overcome by unexpectedly superior numbers and a tactical surprise and, ultimately, annihilated by the Goths; an unswerving commitment to following 'the symptoms' can lead the clinician and investigator alike into many an ambush.

ENTER THE GOTHS AND HUNS

> *Ancient Rome was as confident of the immutability of its world and the continual expansion and improvement of the human lot as we are today* (Arthur Erickson)
> *Language is a city to the building of which every human being brought a stone* (Ralph Waldo Emerson).

As already acknowledged, the Rome process has promoted the cause of IBS and its time course has, not coincidentally, witnessed a tremendous explosion in research on this long-ignored condition. Rome, however, has its baggage and is certainly not infallible! It is evident, for example, that the application of the different Rome criteria results in very different study populations, Rome II, in particular, yielding a very restricted and pain-focused group of IBS patients. This selectivity has, undoubtedly, had a significant impact on the outcome of clinical trials and has, inevitably, resulted in the inclusion of patient populations which were not representative of IBS in the real world.

Though never their primary goal, the Rome criteria have never assumed widespread coinage in clinical practice, simpler, more accessible concepts such as the Manning criteria[10] and the American College of Gastroenterology Guidelines[11] being more amenable to use in clinical practice. Here again the focus, in Rome, on pain has failed to resonate with clinicians whose patients may be more troubled by bloating, bowel difficulties or distension.[12] The laudable approach of Kruis and colleagues of combining symptom analysis with simple and inexpensive tests, such as blood count, sedimentation rate and stool hemoccult,[13] has also been forgotten by Rome while still widely practiced by the practitioner. Though this approach is scarcely supported by clinical data one could argue that it has not been adequately assessed in 'real life' and, in my opinion, deserves re-evaluation, given the availability of new tests such as serum levels of C-reactive protein and stool assays for calprotectin. It should come as no surprise that the Rome criteria have never achieved widespread use in clinical practice; a major indictment of their relevance to real life.

Longitudinal studies have attested to the integrity of diagnoses based on Rome criteria and studies of pathophysiology of IBS performed on Rome-selected patient groups have produced some relatively consistent results. However, it has been from beyond the margins of Rome and from among the barbarian hordes that the latest insights into IBS have come and the promise of a biomarker (or biomarkers) has emerged. The path which led to the formal recognition of postinfectious IBS (PI-IBS) originated in clinical observations which long pre-dated Rome, only to be confirmed in more recent, careful, longitudinal studies which prospectively followed individuals who had been exposed to bacterial gastroenteritis.[14]

Evidence of immune activation and even frank low-grade inflammation have begun to accumulate from studies of various IBS populations exclusive of PI-IBS and the potential for remote infections or infestations to trigger, via immune activation, long-standing dysmotility and sensory neural activation and even phenotypic changes in components of the enteric neuromuscular apparatus provide a firm scientific basis for the concept of inflammatory mediation of IBS-like gut dysfunction.[15,16] That bacterial induction of these changes may occur outwith the context of PI-IBS has been proposed by those who report either qualitative alterations in the colonic microbiota or quantitative changes in the small intestinal flora

(small intestinal bacterial overgrowth – SIBO).[17] The debate which currently rages surrounding the prevalence of SIBO in IBS and the appropriateness of a antibiotic therapy provides a vivid example of the limitations of symptom-based algorithms, such as the Rome process. A failure to recognize the limited symptomatic repertoire of the gut and thus the non-specificity of complaints such as pain, bloating and bowel dysfunction has created the illusion that SIBO is a cause of IBS; the limitations of the diagnostic methods employed to diagnose SIBO notwithstanding, it is simply inappropriate to apply a blanket diagnosis of IBS to those who may harbour some evidence of SIBO. Rather than exposing large numbers of IBS patients to unnecessary and, perhaps, risky antibiotic therapy, the basis for SIBO in patients with supposed SIBO should be assiduously sought. It may well be that these individuals correspond to those IBS patients reported some years ago as exhibiting small intestinal dysmotility and may, therefore, more appropriately belong among one of the motility syndromes proposed by Wingate and colleagues.[18] A slavish adherence to the Rome criteria may well have blinded us to identifying within the vast and undoubtedly heterogeneous population who fulfil its criteria, in their various incarnations, groups of patients who have distinct pathologies? Were it not for the clinical acumen of some clinicians would collagenous and lymphocytic colitis not still be referred to as either D-IBS or 'functional diarrhoea'? Indeed, I would go so far as to say that 'real' diarrhoea should never be accepted as IBS, unless it has been thoroughly evaluated, an assertion supported by recent data emphasizing the difficulty of differentiating, on the basis of symptoms alone, between these entities.[19]

ROME STUMBLES: CRACKS IN THE EDIFICE

Several factors conspired together to precipitate the eventual downfall of the Roman empire and many more, such as a decline in moral values, proposed only to be found wanting for lack of evidence. I have identified a number of cracks in the edifice of the Rome process for the identification of FGIDs that individually and collectively signal its demise.

1 Rome went too far and created disorders for which there is no independent confirmation (be it on the basis of demographics, epidemiology, pathophysiology or response to treatment) of their existence. For most, if not all, of these conditions, the demographics and clinical characteristics are remarkably alike and the therapeutic approach similarly bereft of new approaches; I would argue that they are more alike than distinct.

2 Attempts to further subtype Rome diagnoses have exposed the limitations of symptom-based definitions and led to diagnostic confusion and therapeutic dead ends.

3 There are, at the very least, hints out there that some of those who would, according to Rome, be labelled as IBS may harbour a variety of morphological and other abnormalities; symptoms are too non-specific to allow us to differentiate such phenomena. Progress here will not be advanced, therefore, by further dissections of symptoms but rather by the application of clinical science in all its dimensions.

4 Critically, the failure of Rome-based studies to presage therapeutic advances coupled with the clinically unwieldy nature of the criteria themselves, have impeded their adoption in clinical practice. Quite simply, they are not widely used in the diagnosis of IBS.

What then is the way ahead? I would suggest that progress in IBS and the FGIDs demands the following.

1 An accurate definition of the IBS phenotype(s) coupled with concerted efforts to associate it with putative biomarkers (be they genetic, serological, histological, immunological or physiological). The diagnosis of GORD, for decades based on symptoms alone, has come to be refined by the application of physiological and histological studies; GORD, however, benefits from the presence of an effective therapy thus allowing treatment responsiveness to further support its diagnosis.

> *Assiduus usus uni rei deditus et ingenium et artem saepe vincit*
> ('Constant practice devoted to one subject often outdoes both intelligence and skill', Cicero).

2 The performance of repeated evaluations of phenotype and biomarkers in longitudinal studies. Like GORD, longitudinal studies in IBS are remarkably few despite the high prevalence of both disorders.

3 A re-assessment of the necessity for, or appropriateness of, many of the functional disorders. It is my prediction that, ultimately, most of these entities will be seen to be a part of the spectrum of IBS which will, in turn, come to be recognized as comprising two principal categories of disorder.

a Those symptoms that represent the varying expressions of stress and psychological pain on an essentially normal gut. Stress, be it physical or psychological, leads, in vulnerable individuals, to hypersensitivity and related phenomena with

symptoms being precipitated by physiological stimuli (e.g. acid, the flora, stool and gas).

b A number of, as yet inadequately delineated, 'organic' syndromes lost within that vague catch-all that is IBS (e.g. PI-IBS, ultra microscopic entero-colitis, 'minor' dysmotility and distal SIBO).

It is, therefore, time to marvel and be thankful for what Rome has left us, (the Coliseum, its culture, the precision of Latin and an appreciation of the prevalence of FGIDs and their impact), and move on! It is time to sack Rome and follow the Hun.

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