



The “Organification” of Functional GI Disorders: Implications for Research

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I recently attended an international meeting that focused on potential new mechanisms to help understand the functional gastrointestinal (GI) disorders. It was exciting to hear experts address new concepts on how:

- 1) mucosal inflammation could alter neurotransmitter, ion channel, or nerve growth factor activity and early gene expression, all of which might influence motility and visceral sensation;
- 2) distention of in series tension-sensitive mechanoreceptors in the proximal gastric fundus may lead to dyspeptic symptoms;
- 3) animal models now exist to show that chemical stimulation of gut mucosa alters visceral sensitivity, and can even be modified via descending input from higher brain centers; and
- 4) early genetic studies suggest that 5HT or G-protein receptor polymorphisms may help explain the variability in the clinical expression of irritable bowel syndrome (IBS) or in the response to pharmacological agents.

The organizers are to be congratulated for their foresight, almost 4 years ago, to plan the topics for this meeting. There is little question that some important scientific advances have recently occurred that may lead to greater understanding of the basic mechanisms underlying these disorders, and this is likely to improve treatment.

But is this enough? At this meeting, I also heard comments such as: “At last we have ‘organified’ IBS,” “Now that we have an animal model, we can find a cure,” and “Surely it will now be easier to get research funding.” Implicit in these statements is an assumption that knowledge of the basic mechanisms underlying neuroenteric reactivity or symptom generation is all that is needed to understand our patients with functional GI disorders. At a deeper level, I believe that there is a shared and perhaps desperate concern that unless we “legitimize” research in the functional GI disorders by further prioritizing basic and translational research, we will not be able to “cure” the patients, nor will investigators not involved in basic research be acknowledged for their scientific accomplishments or be funded. While all of this may be true, I believe the logic is misdirected.

The beliefs leading to these statements are intrinsic to the mores of modern Western science, although they are not necessarily held in other cultures, or even in Western society prior to a few hundred years ago. These beliefs were most influenced through the writings of Descartes and relate to the concept of biomedical reductionism. This concept holds that disease (i.e., structural or functional abnormalities of tissues and organs) and illness (i.e., the patients perception of ill health) are understood in terms of linear causality. In other words, the existence of an etiological factor (e.g., an



altered gene, or an infection) is both necessary and sufficient to explain disease, and the disease is necessary and sufficient to explain illness.

Although the reader may tacitly accept this concept as valid, it is in fact only a theory that has so permeated our scientific establishment that it seems unthinkable to be challenged. However, while biomedical investigation is of great value in explaining the basic mechanisms of disease, it is not a practical means to understand human illness. Most clinical symptoms that patients bring to physicians are not explained by specific diseases. Furthermore, medical disease, when present, exhibits immense variability in its clinical expression across individuals so afflicted. Persons with inflammatory bowel or acid peptic disease may vary from having none to severe symptoms, given the same degree of disease localization and activity, and successful treatment of the disease may still be associated with retention of symptoms. This can often be explained by alterations in peripheral or central regulatory mechanisms that influence perception of visceral afferent signals. Interestingly, one important concept that emerged from this meeting is that the functional GI disorders (now designated by the ROME committees as disorders of GI function) are not diseases per se, but rather are clusters of symptoms (i.e., illnesses) that result from a complex interplay of peripheral, central, and environmental factors interacting on the brain-gut axis, and they do so to different degrees across individuals and even for the same individual over time.

Thus, as perhaps most clinicians know, it is not likely that an altered gene or set of specific biological etiologies will explain these complex human disorders, let alone their treatments. Furthermore, if there were major breakthroughs in basic or translational research, their clinical application may take years, if not decades, to bear relevancy. There are major health care needs that need to be addressed now. For the moment, the clinician must appraise, within a clinical context, the degree to which any of several physiological determinants (e.g., visceral hypersensitivity, dysmotility, postinfectious inflammation, psychosocial factors, or any combination) explain the clinical presentation, and this will determine the proper set of treatments.

So if knowledge of the basic mechanisms of GI motor and neuroenteric function is not sufficient to explain the complexity of these human illnesses and does not currently meet the needs of clinicians or their patients, what else can be done? What is also needed is good clinical research that seeks to understand the biopsychosocial interactions affecting the illness experience and health behaviors of our patients, and applies this information in treatment. This would include:

- 1) research on the biological and physiological (gut and brain) influences on symptom experience and behavior and the factors that modulate these outcomes;
- 2) the study of coping and adaptation to chronic illness, outcome, and health services research to help physicians identify more efficient and economic treatment methods for patients;
- 3) clinical trials of pharmaceutical and behavioral treatments to reduce symptoms and improve



quality of life;

- 4) research on educational methods to help health care providers become more efficient, compassionate, and knowledgeable about their patients; and
- 5) helping patients find the ways to help themselves.

Finally, we must demonstrate that human investigational research is equal in its relevancy and legitimacy to basic science research, and needs to be treated as such. The key is through the application of sound and rigorous scientific methodology. One way to accomplish this is to increase the exposure of well-designed clinical studies, which can serve as templates for young investigators looking toward careers in clinical investigation. With Dr. David Brenner's leadership as editor of *GASTROENTEROLOGY* since 2001, the journal has been proactive in encouraging the publication of scientifically rigorous clinical studies. Furthermore, the launching of the new AGA journal *Clinical Gastroenterology and Hepatology* edited by Dr. Michael Camillieri will provide an additional access point for such publications. We are hopeful that in the future, a partnership will exist between basic and clinical investigation such that both will be meeting the needs of our patients and will be receiving equal recognition and support.

References:

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