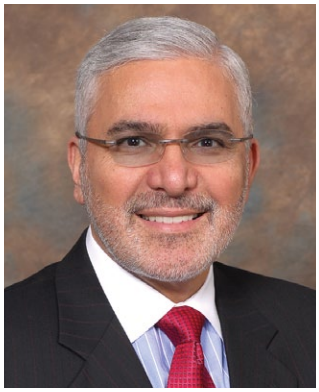

Henry A. Nasrallah, MD
Editor-in-Chief

Psychoneurogastroenterology: The abdominal brain, the microbiome, and psychiatry

Existence of a gastrointestinal (GI) nervous system, distinct from the CNS that comprises the brain and spinal cord, has been recognized for more than a century[1]—yet it has been ignored by psychiatry and rarely is included in residency training.

This nervous system is located inside the wall of the GI tract, extending from the esophagus to the rectum. Technically, it is known as the *enteric nervous system*, or ENS, but it has been given other labels, too: "second brain,"[2] "abdominal brain," "other brain," and "back-up brain." Its neurologic disorders include abdominal epilepsy, abdominal migraine, and autism with intestinal symptoms, such as chronic enterocolitis.[3]

Impressive brain-like features

The ENS includes 100 million neurons (same as the spinal cord) with glia-like support cells. It contains >30 neurotransmitters, including several closely linked to psychopathology (serotonin, dopamine, γ-aminobutyric acid, and acetylcholine). The ENS is not part of the autonomic nervous system. It communicates with the brain via the vagus nerve.

A vast system of gut bacteria

The ENS maintains close links with, and is influenced by, the *microbiome*, an extensive universe of commensal (that is, symbiotic) bacteria in the gut that play a vital role in immune health, brain function, and signaling systems within the CNS. The role of the microbiome in neuropsychiatric disorders has become a sizzling area of research.

The numbers of the microbiome are astonishing, including approximately 1,000 species of bacteria; 100 trillion total bacterial organisms (outnumbering cells of the body by 100-fold); 4 million bacterial genes (compared with 26,000 genes in the host human genome); and a density as high as 1 trillion bacteria in a cubic milliliter—higher than any known microbial system.[4]

Significant GI–brain connections

It is of great relevance to psychiatry that 90% of the body's serotonin and 50% of dopamine are found in the GI brain. Selective serotonin reuptake inhibitors often are associated with GI symptoms, such as nausea and diarrhea; antipsychotics, which are dopamine antagonists, are known for antiemetic effects. Clozapine's potent anticholinergic effects can cause serious ileus.

Things get more interesting when one considers the association of GI disorders and psychiatric symptoms:

Irritable bowel syndrome is associated with panic disorder, generalized anxiety

Neuropsychiatric researchers have long ignored the enteric nervous system and the microbiome; it's time for them to focus on how to exploit these entities

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disorder, social phobia, dysthymia, and major depression.

Inflammatory bowel disease (IBD)—such as Crohn's disease and ulcerative colitis (prevalence ranging from 6% in Canada to 14% in the United States to 46% in Mexico[5])—is commonly associated with mood and anxiety disorders and personality changes. The psychiatric manifestations of IBD are so common that the authors of a recent article in *World Journal of Gastroenterology* urged gastroenterologists to collaborate with psychiatrists when managing IBD.[6]

Celiac disease has been repeatedly associated with several neuropsychiatric disorders, including ataxia, epilepsy, peripheral neuropathy, headache, anxiety, attention-deficit/hyperactivity disorder, autism spectrum disorder, and schizophrenia.

New, exciting challenges for medical science

There potentially are important implications for possible exploitation of the ENS and the microbiome in the diagnosis and treatment of neuropsychiatric disorders. For example, consider these speculative challenges:

- Can intestinal biopsy reveal neurotransmitter pathology in schizophrenia?
- Can early dopamine deficiency predict Parkinson's disease, enabling early intervention?
- Can β-amyloid deposits, the degenerative neurologic stigmata of Alzheimer's disease, be detected in abdominal neurons years before onset of symptoms to allow early intervention?
- Can the ENS become a therapeutic pathway by targeting the various neurotransmitters found there or by engaging the enormous human microbiome to manipulate its beneficial properties?
- Can foods or probiotic supplements be prescribed as microbiomal adjuncts to improve the mood and anxiety spectrum?

One recommendation I came across is that ingesting 10 to 100 million beneficial bacteria, such as *Lactobacillus plantarum* and *Bifidobacterium infantis*, might be helpful. Such prescriptions obviously are speculative but also are reasonably testable hypotheses of ways to exploit the "other brain" and the microbiome.

We must summon the guts to seize this opportunity

An independent second brain and a remarkable microbiome appear to be significant evolutionary adaptations and advantages for humans. For too long, neuropsychiatric researchers have ignored the ENS and the microbiome; now, they must focus on how to exploit these entities to yield innovative diagnostic and therapeutic advances. Integrating the ENS and the microbiome and enmeshing them into neuropsychiatric research and clinical applications hold great promise.

The field of psychoneurogastroenterology is in its infancy, but its growth and relevance will be momentous for neuropsychiatry. A major intellectual peristalsis is underway.

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Published through an educational partnership with Saint Louis University
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