

## The Other Brain Also Deals With Many Woes

by Harriet Brown

Two brains are better than one. At least that is the rationale for the close - sometimes too close - relationship between the human body's two brains, the one at the top of the spinal cord and the hidden but powerful brain in the gut known as the enteric nervous system.

For Dr. Michael D. Gershon, the author of "The Second Brain" and the chairman of the department of anatomy and cell biology at Columbia, the connection between the two can be unpleasantly clear. "Every time I call the National Institutes of Health to check on a grant proposal," Dr. Gershon said, "I become painfully aware of the influence the brain has on the gut."

In fact, anyone who has ever felt butterflies in the stomach before giving a speech, a gut feeling that flies in the face of fact or a bout of intestinal urgency the night before an examination has experienced the actions of the dual nervous systems.

The connection between the brains lies at the heart of many woes, physical and psychiatric. Ailments like anxiety, depression, irritable bowel syndrome, ulcers and Parkinson's disease manifest symptoms at the brain and the gut level.

"The majority of patients with anxiety and depression will also have alterations of their GI function," said Dr. Emeran Mayer, professor of medicine, physiology and psychiatry at the University of California, Los Angeles.

A study in 1902 showed changes in the movement of food through the gastrointestinal tract in cats confronted by growling dogs.

One system's symptoms - and cures - may affect the other. Antidepressants, for example, cause gastric distress in up to a quarter of the people who take them. Butterflies in the stomach are caused by a surge of stress hormones released by the body in a "fight or flight" situation. Stress can also overstimulate nerves in the esophagus, causing a feeling of choking.

Dr. Gershon, who coined the term "second brain" in 1996, is one of a number of researchers who are studying brain-gut connections in the relatively new field of neurogastroenterology. New understandings of the way the second brain works, and the interactions between the two, are helping to treat disorders like constipation, ulcers and Hirschprung's disease.

The role of the enteric nervous system is to manage every aspect of digestion, from the esophagus to the stomach, small intestine and colon. The second brain, or little brain, accomplishes all that with the same tools as the big brain, a sophisticated nearly self-contained network of neural circuitry, neurotransmitters and proteins.

The independence is a function of the enteric nervous system's complexity.

"Rather than Mother Nature's trying to pack 100 million neurons someplace in the brain or spinal cord and then sending long connections to the GI tract, the circuitry is right next to the systems that require control," said Jackie D. Wood, professor of physiology, cell biology and internal medicine at Ohio State.

Two brains may seem like the stuff of science fiction, but they make literal and evolutionary sense.

"What brains do is control behavior," Dr. Wood said. "The brain in your gut has stored within its neural networks a variety of behavioral programs, like a library. The digestive state determines which program your gut calls up from its library and runs."

When someone skips lunch, the gut is more or less silent. Eat a pastrami sandwich, and contractions all along the small intestines mix the food with enzymes and move it toward the lining for absorption to begin. If the pastrami is rotten, reverse contractions will force it - and everything

else in the gut - into the stomach and back out through the esophagus at high speed.

In each situation, the gut must assess conditions, decide on a course of action and initiate a reflex.

"The gut monitors pressure," Dr. Gershon said. "It monitors the progress of digestion. It detects nutrients, and it measures acid and salts. It's a little chemical lab."

The enteric system does all this on its own, with little help from the central nervous system.

The enteric nervous system was first described in 1921 by Dr. J. N. Langley, a British physician who believed that it was one of three parts - along with the parasympathetic and sympathetic nervous systems - of the autonomic nervous system, which controls involuntary behaviors like breathing and circulation. In this triad, the enteric nervous system was seen as something of a tag-along to the other two.

After Langley died, scientists more or less forgot about the enteric nervous system. Years later, when Dr. Gershon reintroduced the concept and suggested that the gut might use some of the same neurotransmitters as the brain, his theory was widely ridiculed.

"It was like saying that New York taxi drivers never miss a showing of 'Tosca' at the Met," he recalled.

By the early 80's, scientists had accepted the idea of the enteric nervous system and the role of neurotransmitters like serotonin in the gut.

It is no surprise that there is a direct relationship between emotional stress and physical distress. "Clinicians are finally acknowledging that a lot of dysfunction in GI disorders involves changes in the central nervous system," said Gary M. Mawe, a professor of anatomy and neurobiology at the University of Vermont.

The big question is which comes first, physiology or psychology?

The enteric and central nervous systems use the same hardware, as it were, to run two very different programs. Serotonin, for instance, is crucial to feelings of well-being. Hence the success of the antidepressants known as S.S.R.I.'s

that raise the level of serotonin available to the brain.

But 95 percent of the body's serotonin is housed in the gut, where it acts as a neurotransmitter and a signaling mechanism. The digestive process begins when a specialized cell, an enterochromaffin, squirts serotonin into the wall of the gut, which has at least seven types of serotonin receptors. The receptors, in turn, communicate with nerve cells to start digestive enzymes flowing or to start things moving through the intestines.

Serotonin also acts as a go-between, keeping the brain in the skull up to date with what is happening in the brain below. Such communication is mostly one way, with 90 percent traveling from the gut to the head.

Many of those messages are unpleasant, and serotonin is involved in sending them. Chemotherapy drugs like doxorubicin, which is used to treat breast cancer, cause serotonin to be released in the gut, leading to nausea and vomiting. "The gut is not an organ from which you wish to receive frequent progress reports," Dr. Gershon said.

Serotonin is also implicated in one of the most debilitating gut disorders, irritable bowel syndrome, or I.B.S., which causes abdominal pain and cramping, bloating and, in some patients, alternating diarrhea and constipation.

"You can run any test you want on people with I.B.S., and their GI tracts look essentially normal," Dr. Mawe said. The default assumption has been that the syndrome is a psychosomatic disease.

But it turns out that irritable bowel syndrome, like depression, is at least in part a function of changes in the serotonin system. In this case, it is too much serotonin rather than too little.

In a healthy person, after serotonin is released into the gut and initiates an intestinal reflex, it is whisked out of the bowel by a molecule known as the serotonin transporter, or SERT, found in the cells that line the gut wall.

People with irritable bowel syndrome do not have enough SERT, so they wind up with too much serotonin floating around, causing diarrhea.

The excess serotonin then overwhelms the receptors in the gut, shutting them down and causing constipation.

When Dr. Gershon, whose work has been supported by Novartis, studied mice without SERT, he found that they developed a condition very much like I.B.S. in humans.

Several new serotonin-based drugs - intestinal antidepressants, in a way - have brought hope for those with chronic gut disorders.

Another mechanism that lends credence to physiology as the source of intestinal dysfunctions is the system of mast cells in the gut that have an important role in immune response.

"During stress, trauma or 'fight or flight' reactions, the barrier between the lumen, the interior of the gut where food is digested, and the rest of the bowel could be broken, and bad stuff could get across," Dr. Wood said. "So the big brain calls in more immune surveillance at the gut wall by activating mast cells."

These mast cells release histamines and other inflammatory agents, mobilizing the enteric nervous system to expel the perceived intruders, and causing diarrhea.

Inflammation induced by mast cells may turn out to be crucial in understanding and treating GI disorders. Inflamed tissue becomes tender. A gut under stress, with chronic mast cell production and consequent inflammation, may become tender, as well.

In animals, Dr. Mawe said, inflammation makes the sensory neurons in the gut fire more often, causing a kind of sensory hyperactivity. "I have a theory that some chronic disorders may be caused by something like attention deficit disorder in the gut," he said.

Dr. Gershon, too, theorizes that physiology is the original culprit in brain-gut dysfunctions. "We have identified molecular defects in the gut of everyone who has irritable bowel syndrome," he said. "If you were chained by bloody diarrhea to a toilet seat, you, too, might be depressed."

Still, psychology clearly plays a role. Recent studies suggest that stress, especially early in life, can cause chronic GI diseases, at least in animals. "If you put a rat on top of a little platform surrounded by water, which is very stressful for a rat, it develops the equivalent of diarrhea," Dr. Mayer said.

Another experiment showed that when young rats were separated from their mothers, the layer of cells that line the gut, the same barrier that is strengthened by mast cells during stress, weakened and became more permeable, allowing bacteria from the intestine to pass through the bowel walls and stimulate immune cells.

"In rats, it's an adaptive response," Dr. Mayer said. "If they're born into a stressful, hostile environment, nature programs them to be more vigilant and stress responsive in their future life."

He said up to 70 percent of the patients he treats for chronic gut disorders had experienced early childhood traumas like parents' divorces, chronic illnesses or parents' deaths. "I think that what happens in early life, along with an individual's genetic background, programs how a person will respond to stress for the rest of his or her life," he said.

Either way, what is good for one brain is often good for the other, too. A team of researchers from Penn State University recently discovered a possible new direction in treating intestinal disorders, biofeedback for the brain in the gut.

In an experiment published in a recent issue of *Neurogastroenterology and Motility*, Robert M. Stern, a professor of psychology at Penn State, found that biofeedback helped people consciously increase and enhance their gastrointestinal activity. They used the brains in their heads, in other words, to help the brains in their guts, proving that at least some of the time two brains really are better than one.