Complex and Hidden Brain in Gut Makes Stomachaches and Butterflies

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EVER wonder why people get "butterflies" in the stomach before going on stage? Or why an impending job interview can cause an attack of intestinal cramps? And why antidepressants targeted for the brain cause nausea or abdominal upset in millions of people who take such drugs?

The reason for these common experiences, scientists say, is that the body has two brains -- the familiar one encased in the skull and a lesser known but vitally important one found in the human gut. Like Siamese twins, the two brains are interconnected; when one gets upset, the other does, too.

The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon. Considered a single entity, it is a network of neurons, neurotransmitters and proteins that zap messages between neurons, support cells like those found in the brain proper and a complex circuitry that enables it to act independently, learn, remember and, as the saying goes, produce gut feelings.

The brain in the gut plays a major role in human happiness and misery. But few people know it exists, said Dr. Michael Gershon, a professor of anatomy and cell biology at Columbia-Presbyterian Medical Center in New York. For years, people who had ulcers, problems swallowing or chronic abdominal pain were told that their problems were imaginary, emotional, simply all in their heads, Dr. Gershon said. They were shuttled to psychiatrists for treatment.

Doctors were right in ascribing these problems to the brain, Dr. Gershon said, but they blamed the wrong one. Many gastrointestinal disorders like colitis and irritable bowel syndrome originate from problems within the gut's brain, he said. And the current wisdom is that most ulcers are caused by a bacterium, not by hidden anger at one's mother.

Symptoms stemming from the two brains get confused, Dr. Gershon said. "Just as the brain can upset the gut, the gut can also upset the brain" he said. "If you were chained to the toilet with cramps, you'd be upset, too."

Details of how the enteric nervous system mirrors the central nervous system have been emerging in recent years, said Dr. Gershon, who is considered one of the founders of a new field of medicine called neurogastroenterology.

Nearly every substance that helps run and control the brain has turned up in the gut, Dr. Gershon said. Major neurotransmitters like serotonin, dopamine, glutamate, norepinephrine and nitric oxide are there. Two dozen small brain proteins, called neuropeptides, are in the gut, as are major cells of the immune system. Enkephalins, one class of the body's natural opiates, are in the gut. And in a finding that stumps researchers, the gut is a rich source of benzodiazepines -- the family of psychoactive chemicals that includes such ever popular drugs as Valium and Xanax.

In evolutionary terms, it makes sense that the body has two brains, said Dr. David Wingate, a professor of gastrointestinal science at the University of London and a consultant at Royal London Hospital. The first nervous systems were in tubular animals that stuck to rocks and waited for food to pass by, Dr. Wingate said. The limbic system is often referred to as the "reptile brain."

As life evolved, animals needed a more complex brain for finding food and sex and so developed a central nervous system. But the gut's nervous system was too important to put inside the newborn head with long connections going down to the body, Dr. Wingate said. Offspring need to eat and digest food at birth. Therefore, nature seems to have preserved the enteric nervous system as an independent circuit inside higher animals. It is only loosely connected to the central nervous system and can mostly function alone, without instructions from topside.

This is indeed the picture seen by developmental biologists. A clump of tissue called the neural crest forms early in embryogenesis, Dr. Gershon said. One section turns into the central nervous system. Another piece migrates to become the enteric nervous system. Only later are the two nervous systems connected via a cable called the vagus nerve.

Until relatively recently, people thought that the gut's muscles and sensory nerves were wired directly to the brain and that the brain controlled the gut through two pathways that increased or decreased rates of activity, Dr. Wingate said. The gut was simply a tube with simple reflexes. Trouble is, no one bothered to count the nerve fibers in the gut. When they did, he said, they were surprised to find that the gut contains 100 million neurons -- more than the spinal cord has. Yet the vagus nerve only sends a couple of thousand nerve fibers to the gut.

The brain sends signals to the gut by talking to a small number of "command neurons," which in turn send signals to gut interneurons that carry messages up and down the pike, Dr. Gershon said. Both command neurons and interneurons are spread throughout two layers of gut tissue called the myenteric plexus and the submuscosal plexus. ("Solar plexus" is actually a boxing term that refers simply to nerves in the abdomen.) Command neurons control the pattern of activity in the gut, Dr. Gershon said. The vagus nerve only alters the volume by changing its rates of firing.

The plexuses also contain glial cells that nourish neurons, mast cells involved in immune responses, and a "blood brain barrier" that keeps harmful substances away from important neurons, Dr. Gershon said. They have sensors for sugar, protein, acidity and other chemical factors that might monitor the progress of digestion, determining how the gut mixes and propels its contents. "It's not a simple pathway," he said. "It uses complex integrated circuits not unlike those found in the brain."

The gut's brain and the head's brain act the same way when they are deprived of input from the outside world, Dr. Wingate said. During sleep, the head's brain produces 90-minute cycles of slow wave sleep punctuated by periods of rapid eye movement sleep in which dreams occur. During the night, when it has no food, the gut's brain produces 90-minute cycles of slow wave muscle contractions punctuated by short bursts of rapid muscle movements, Dr. Wingate said.

The two brains may influence each other while in this state, Dr. Wingate said. Patients with bowel problems have been shown to have abnormal rem sleep. This finding is not inconsistent with the folk wisdom that indigestion can produce nightmare.

As light is shed on the circuitry between the two brains, researchers are beginning to understand why people act and feel the way they do. When the central brain encounters a frightening situation, it releases stress hormones that prepare the body to fight or flee, Dr. Gershon said. The stomach contains many sensory nerves that are stimulated by this chemical surge -- hence the "butterflies." On the battlefield, the higher brain tells the gut brain to shut down, Dr. Gershon said. "A frightened, running animal does not stop to defecate," he said.

Fear also causes the vagus nerve to "turn up the volume" on serotonin circuits in the gut, Dr. Gershon said. Thus overstimulated, the gut goes into higher gear and diarrhea results. Similarly, people sometimes "choke" with emotion. When nerves in the esophagus are highly stimulated, people have trouble swallowing.

Even the so-called "Maalox moment" of advertising fame can be explained by the two brains interacting, said Dr. Jackie D. Wood, chairman of the department of physiology at Ohio State University in Columbus. Stress signals from the head's brain can alter nerve function between the stomach and esophagus, resulting in heartburn.

In cases of extreme stress, Dr. Wood said, the higher brain seems to protect the gut by sending signals to immunological mast cells in the plexus. The mast cells secrete histamine, prostaglandin and other agents that help produce inflammation, he said. "This is protective. If an animal is in danger and subject to trauma, dirty stuff in the intestines is only a few cells away from the rest of the body. By inflaming the gut, the brain is priming the gut for surveillance. If the barrier breaks, the gut is ready to do repairs," Dr. Wood said. Unfortunately, the chemicals that get released also cause diarrhea and cramping.

Such cross talk also explains many drug interactions, Dr. Gershon said. "When you make a drug to have psychic effects on the brain, it's very likely to have an effect on the gut that you didn't think about," he said. Conversely, drugs developed for the brain could have uses in the gut.

For example, the gut is loaded with the neurotransmitter serotonin. When pressure receptors in the gut's lining are stimulated, serotonin is released and starts the reflexive motion of peristalsis, Dr. Gershon said.

Now a quarter of people taking Prozac or similar antidepressants have gastrointestinal problems like nausea, diarrhea and constipation, he said. These drugs act on serotonin, preventing its uptake by target cells so that it remains more abundant in the central nervous system.

In a study to be published soon, Dr. Gershon and his colleagues explain Prozac's side effects on the gut. They mounted a section of guinea pig colon on a stand and put a small pellet in the "mouth" end. The isolated colon whips the pellet down to the "anal" end of the column, just as it would inside an animal, Dr. Gershon said.

When the researchers put a small amount of Prozac into the colon, the pellet "went into high gear," Dr. Gerhson said. The drug doubled the speed at which the pellet passed through the colon, which would explain why some people get diarrhea. Prozac has been used in small doses to treat chronic constipation, he said.

But when researchers increased the amount of Prozac in the guinea pig colon, the pellet stopped moving. The colon froze up, Dr. Gershon said, which is why some people get constipated on the drug. And because Prozac stimulated sensory nerves, he said, it can also cause nausea.

Some antibiotics like erythromycin act on gut receptors to produce oscillations, Dr. Gershon said. People experience cramps and nausea. Drugs like morphine and heroin attach to the gut's opiate receptors, producing constipation. Indeed, both brains can be addicted to opiates.

Victims of Alzheimer's and Parkinson's diseases suffer from constipation. The nerves in their gut are as sick as the nerve cells in their brains.

Just as the central brain affects the gut, the gut's brain can talk back to the head, Dr. Gershon said. Most of the gut sensations that enter conscious awareness are negative things like pain and bloatedness, Dr. Wingate said. People do not expect to feel anything good from the gut but that does not mean such signals are absent, he said.

Hence, the intriguing question: why does the human gut produce benzodiazepine? The human brain contains receptors for benzodiazepine, a drug that relieves anxiety, suggesting that the

body produces its own internal source of the drug, said Dr. Anthony Basile, a neurochemist in the Neuroscience Laboratory at the National Institutes of Health in Bethesda, Md. Several years ago, he said, an Italian scientist made a startling discovery. Patients with liver failure fall into a deep coma. The coma can be reversed, in minutes, by giving the patient a drug that blocks benzodiazepine.

When the liver fails, substances usually broken down by the liver get to the brain, Dr. Basile said. Some are bad, like ammonia and mercaptans, which are "smelly compounds that skunks spray on you," he said. But a series of compounds are also identical to benzodiazepine. "We don't know if they come from gut itself, from bacteria in the gut or from food," Dr. Basile said. But when the liver fails, the gut's benzodiazepine goes straight to the brain, knocking the patient unconscious.

The payoff for exploring gut and head brain interactions is enormous, Dr. Wood said. For example, many people are allergic to certain foods, like shellfish. This is because mast cells in the gut mysteriously become sensitized to antigens in the food. The next time the antigen shows up in the gut, Dr. Wood said, the mast cells call up a program, releasing chemical modulators that try to eliminate the threat. The allergic person gets diarrhea and cramps, he said.

Many autoimmune diseases like Krohn's disease and ulcerative colitis may involve the gut's brain, Dr. Wood said. The consequences can be horrible, as in Chagas disease, which is caused by a parasite found in South America. Those infected develop an autoimmune response to neurons in their gut, Dr. Wood said. Their immune systems slowly destroy their own gut neurons. When enough neurons die, the intestines literally explode.

A big question remains. Can the gut's brain learn? Does it "think" for itself? Dr. Gershon tells a story about an old Army sergeant, a male nurse in charge of a group of paraplegics. With their lower spinal cords destroyed, the patients would get impacted.

"The sergeant was anal compulsive," Dr. Gershon said. "At 10 A.M. everyday, the patients got enemas. Then the sergeant was rotated off the ward. His replacement decided to give enemas only after compactions occurred. But at 10 the next morning, everyone on the ward had a bowel movement at the same time, without enemas," Dr. Gershon said. Had the sergeant trained those colons?

The human gut has long been seen as a repository of good and bad feelings. Perhaps emotional states from the head's brain are mirrored in the gut's brain, where they are felt by those who pay attention to them.