The wisdom of the gut

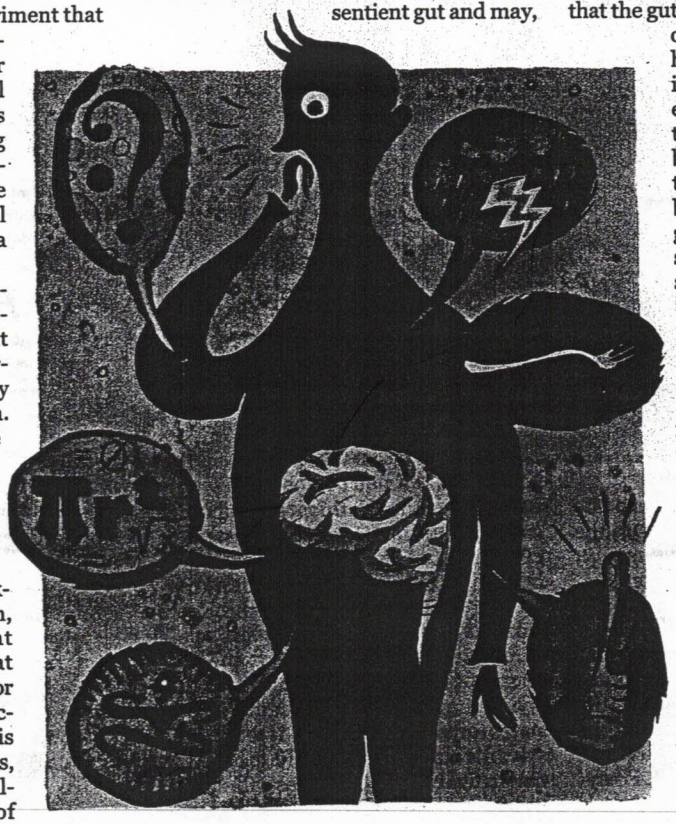
Those butterflies in your stomach are not just in your mind

BY RACHEL K. SOBEL

In 1917, German scientist Paul Trendelenburg huddled over a test tube in his three-story laboratory, prodding a small section of tissue submerged in the body's natural juices. Forced to stay home from the war because of tuberculosis, this budding pharmacologist poured his energies into designing the experiment that would prove what his scientific forefathers had suspected for years. Embedded within the wall of the gut, he would show, was a self-contained, self-regulating nervous system that could function on its own, without the help of the brain or the spinal cord. The gut, in short, had a mind of its own.

For reasons that still mystify researchers today, the stunning results of this experiment went into hibernation for nearly half a century and are only now receiving fresh validation. Indeed, no one in medicine paid attention again until a fledgling neurobiologist began touting its clinical value in 1965. "The idea that the gut can be operating its own nervous system was shocking," recalls Michael Gershon, now chair of the department of anatomy and cell biology at Columbia University and author of *The Second Brain*, a 1998 account of the acceptance of this scientific idea. Since the 1980s, Gershon's colleagues have zealously embraced the notion of "the little brain in the gut," as it's affectionately known. "What Mother Nature had done, rather than packing all of those neurons in the big brain in the skull and sending long lines to the gut, is distribute the microcomputer, the little brain, right along with the gut," says Jackie Wood, a neurobiologist at Ohio State University.

Now a full-blown renaissance in neurogastroenterology—the nine-syllable code word for the study of the nerves entrenched in the lining of the esophagus, stomach, small intestine, and colon—has researchers probing the depths of the digestive nervous system with feverish intensity and surfacing with remarkable insights. This new breed of neuroscientist, 300 strong, and counting, is shaping a novel notion of the gut and deriving innovative ways to treat its ailments. Last month, for example, the first drug ever designed for irritable-bowel syndrome (IBS), called Lotronex, arrived in doctors' offices. It's based on this new understanding of the sentient gut and may, in fact, change the way physicians handle this and related disorders.



Daily chores. By peeling away the layers of padding that surround the digestive tract, scientists have indeed unearthed some of the buried secrets of the little brain. This miniature central processing unit, whose 100 million-plus nerves number more than those in the spinal cord, carries out many of its daily chores without guidance from the brain. "Suppose the gut gets a message that the pressure is up in the stomach. The brain doesn't get its hands dirty with that kind of nonsense—so the gut takes care of it," explains Gershon. Not only does the gut direct its own show, he adds, but its spidery projections trickle into neighboring organs, commanding the pancreas and gallbladder to aid with digestion.

Though able to run itself, the little brain does stay in close touch with the big brain via 1,000 or so nerve fibers. Scientists studying this relationship have discovered that the gut-brain connection is at the heart of some of the most visceral human emotions. A "gut feeling," for example, isn't just a poetic conceit used to convey intuition. It arises from the biological interplay between these two intimately connected brains, says Emeran Mayer, a gastroenterologist and professor of physiology at the University of California–Los Angeles. When faced with an anxiety-ridden situation, the big brain sends urgent messages to the little brain, which begins orchestrating a physical response, read as gurgling or "butterflies" in the stomach. These sensations are recorded in an "emotional memory bank" residing in the big brain, says Mayer, and the next time the big brain makes a decision in a similar situation, it's not based on some intellectual calculation. Rather, it's instantaneously formulated from this catalog of previous bodily responses—"gut feelings"—stored in the brain.

Why some people feel the burden of stress in their gut—and not for instance, in their heart—can also be explained by the close communication between the brain and the gut. When the big brain consciously perceives a stressful situation, it calls on its fraternal twin through specialized cells—called mast cells—embedded in the gut's lining. These mast cells secrete a chemical called histamine, which activates the nerves controlling the gut, telling the muscles to contract. Hence, the cramps and bathroom trips so often associated with bouts of stress.

The complex circuitry in the gut not only operates like a brain; it looks uncannily similar to one, too. Just like the nerves

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in the brain and spinal cord, those in the gut are naked, lacking an insulating sheath that wraps around the rest of the body's nerves. Swishing among the gut's nerves are serotonin, nitric oxide, carbon monoxide, and at least 30 other neurochemicals—the same ones sloshing around in the skull. Curiously enough, as healthy brains in the head and gut resemble each other, so too do diseased ones. Scientists have found that some Alzheimer's and Parkinson's patients accumulate the same type of tissue damage in their bowels as they do in their skulls, raising the possibility that these disorders might someday be diagnosed by routine rectal biopsy.

No-brainer. The fact that the two brains share so much of the same biology can explain why psychiatric medications have side effects in the gut. Antidepressants like Prozac, for instance, increase the presence of serotonin in the spaces where nerves talk to each other in both brains. While this neurochemical shift settles the big brain emotionally, it causes the gut to squirm, leading to side effects like abdominal cramping and diarrhea.

Many investigators are taking their cues in treating gut disorders from drugs that have worked on the brain. For example, Michael Camilleri, a gastroenterologist at the Mayo Clinic, is treating a variety of gastrointestinal disorders with Clonidine, a drug sometimes used in psychiatry. Another medication called Imitrex, customarily used to soothe the pangs of migraine headaches, has effectively healed the gut in two studies by Belgian teams. And Lotronex, the recently released treatment for irritable-bowel syndrome, came from an anti-anxiety drug.

If the arrival of Lotronex signals a new era in treatment, it also goes a long way in debunking the popular notion that IBS is "all in the head." Though IBS is a relatively common disorder, affecting as many as 1 in 5 people, it is difficult to diagnose with conventional methods. The chronic abdominal pain, discomfort, and irregular bowel movements leave no trace in the lining of the gut because such abnormalities presumably occur at the level of the nerves tucked inside the gut. This lack of physiological evidence has led many doctors to dismiss patients' complaints as psychosomatic. It's now hypothesized that the nerves lining the gut are oversensitive and overreact to gas and food passing by, thus causing pain and cramping. "Lotronex suggests that there is a mechanism that is malfunctioning either in the big brain or the little brain, or both, or someplace in between," says Wood. "IBS is not imagined." ●

Teen angels, can you hear this message?

Young drivers plus passengers equals disaster

BY JOHN S. MACNEIL

Most Americans remember earning a driver's license as one of the most empowering events of their young lives, a source of unprecedented freedom and mobility. Unfortunately, this rite of passage also marks the beginning of the most dangerous teenage years. Drivers who are 16 and 17 years old are known to run a much higher risk of being involved in an accident than older drivers. And if that weren't enough, new research now shows that the more teenage passengers in the car, the greater the risk of dying in an accident.

JOHN EASTCOTT AND YVA MOMATIUK—IMAGE WORKS

It's risky to hitch a ride with a 16-year-old driver. ● *Not stupidity, just lack of driving experience*

Although previous studies have hinted at this connection, the most recent study, published in last week's *Journal of the American Medical Association,* offers a starker picture of how risky it is to get a lift from a teenage driver. Indeed, a 16-year-old driver with three or more passengers is three times as likely to have a fatal accident as a teenager driving alone. By contrast, the risk of death for drivers between 30 and 59 decreases with each additional passenger.

The authors also found that the death rates for teenage drivers increased dramatically after 10 p.m., and especially after midnight. With passengers in the car, the driver was even more likely to die in a late-night accident.

Robert Foss, a scientist at the University of North Carolina Highway Safety Research Center and author of an editorial accompanying the study, says the higher death rates for teenage drivers have less to do with "really stupid behavior" than with just lack of driving experience. "The basic issue," he says, "is that adults [who are responsible for issuing licenses] fail to recognize how complex and skilled a task driving is."

Graduated licensing. Both he and the author of the study, Johns Hopkins University researcher Li-Hui Chen, believe that the way to mitigate the problem is to have states institute so-called graduated licensing systems, in which getting a license is a multistage process. A graduated license requires that a teenager first prove himself capable of driving in the presence of an adult, followed by a period of driving with night or passenger restrictions, before graduating to full driving privileges.

Graduated license systems have reduced teenage driver crashes, according to recent studies. About half of the states now have some sort of graduated licensing system in place, but only 10 of those states have restrictions on passengers. California is the strictest, with a novice driver prohibited from carrying any passengers under 20 (without the presence of an adult over 25) for the first six months.

Other unpublished data are even more dramatic, Foss adds. They show that even if every teenager who would have been able to catch a ride were instead to drive his or her own car, there would still be a reduction in the number of teenage driver deaths. "Even though it may put more drivers on the road," he says, "we'll still get a net benefit." ●