# GUT HORMONES

## Recent research suggests that gastrointestinal hormones may be involved in certain digestive diseases, and one may even provide a treatment for obesity

BY JOAN AREHART-TREICHEL

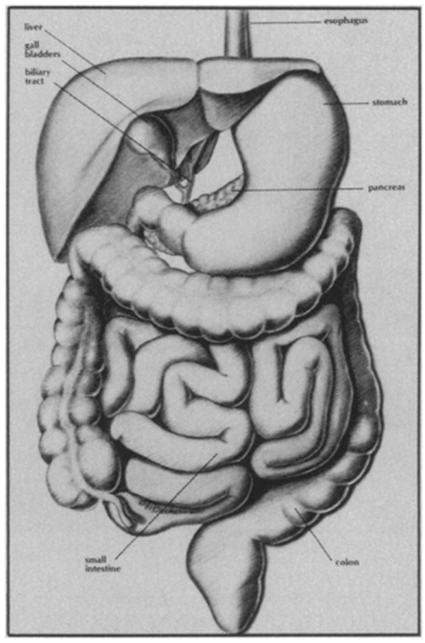
Two years ago a researcher, whom we'll call James Sweet, was eager to see what a gastrointestinal hormone called pancreatic polypeptide (PP) would do if injected into humans. "No way!" his medical school's ethics committee countered. "Because PP has never been tried on humans before, you have to experiment on yourself first." So Sweet, a brave or foolish physiologist (depending on one's viewpoint), lay down on a couch and received an injection of PP.

Sweet started perspiring and felt a tightening across his chest. Was he having a heart attack? he wondered. "And me with a wife and four children!" he thought. Then his co-workers gave him the good news: He had received a placebo. The next time around, though, Sweet got the real stuff, and fortunately for his family its effects were essentially innocuous. With this evidence that PP was safe, other persons volunteered for injections, and PP was found to inhibit pancreatic secretions. Because pancreatic secretions are necessary for digestion, Sweet today jokingly refers to PP as "the gut hormone of indigestion." Whether PP also has a salubrious effect on digestion remains to be determined.

The above true-life episode captures some of the drama underlying a long-neglected but quietly growing area of research—hormones made by the digestive tract, or what are known as "gut hormones." These protein molecules do their work where they are produced or they may be sent to various parts of the body, say from the small intestine to the gall bladder, or from the small intestine to the pancreas via the bloodstream.

Recent research on gut hormones was presented at a Miles symposium on protein hormones at the Johns Hopkins Medical Institutions. It was reported that the hormones may play a role in certain digestive diseases, and that one gut hormone may even prove effective as an anti-obesity drug.

Gut hormones are similar to classic hormones in that they can be secreted by typical endocrine cells (which are present in all digestive tract organs) and exert their effects on tissues at distant sites, explain Julia M. Polak of the Royal Postgraduate Medical School in London and Graham J. Dockray of the University of Liverpool in Liverpool, England. For instance, when the lower part of the stomach is full of food, it secretes a hormone called gastrin into the bloodstream, which then acts on the upper part of the stomach to stimulate acid production there. The hormone known as secretin is made primarily in classic endocrine cells in the 20-foot-long small intestine and acts on the pancreas. The hormone enteroglucagon is made primarily in endocrine cells in the five-foot-long large intestine and acts on the small intestine to stimulate growth.



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Gut hormones mimic classic protein hormones in that they hook up with specific target cell receptors, reports Jerry D. Gardner of the National Institute of Arthritis, Metabolism and Digestive Diseases in Bethesda, Md. For instance, many gut hormones act on pancreatic cell receptors. This action leads, inside the pancreatic cell, to an increase in enzyme secretion caused by a hormone-induced increase in cyclic AMP or in release of calcium. A third way that gut hormones resemble classic hormones, Dockray points out, is that they come in multimolecular forms. "When we speak of, say, gastrin," he says, "we are actually talking about a collection of molecules." A fourth resemblance between gut and conventional protein hormones, he adds, is that they may share certain amino acid sequences with each other or may be formed from the same large precursor molecules. These findings suggest a common evolutionary origin for the gut hormone family.

But gut hormones don't always act in the classic manner. As Dockray and Polak point out, they may be released by nerve cells instead of by endocrine cells and thus serve as communicating chemicals between nerves instead of as hormones. Or they may act as local rather than as long-distance hormonal messengers, as do a family of fatty substances in the body called prostaglandins. And as Gardner points out, gut hormones may be released from a cell and even act on the same cell—a sort of hormonal incest. So, Gardner concludes, "Most of the gut hormones are

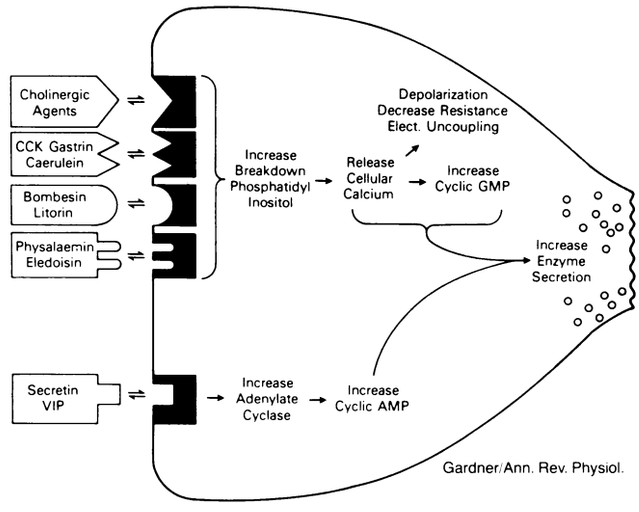



*Diagram illustrates the initial steps of various methods by which different gut hormones act on pancreatic cells.*

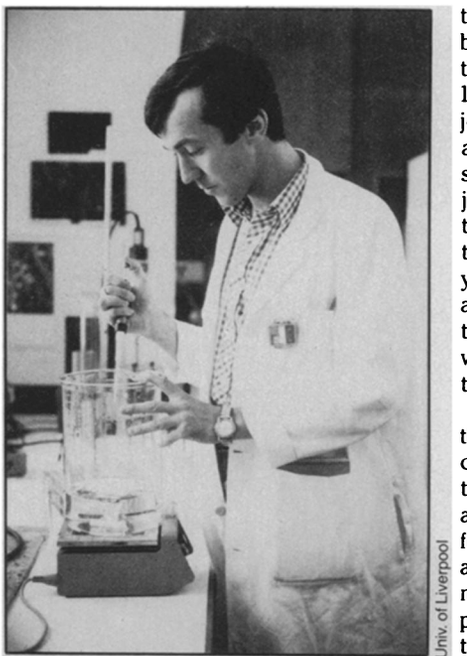
really something other than hormones. Gastrointestinal peptides would be a more appropriate term."

Regardless of their nomenclature, gut hormones are more than a scientific curiosity. As Stephen R. Bloom of the Royal Postgraduate Medical School in London points out, the gut hormone motilin is involved in indigestion. While motilin's normal role is to empty the stomach of food and to keep the stomach free from bacterial growth, it sometimes forces stomach acid up into the esophagus where it creates indigestion. In fact, symposium speakers concurred that as gut hormone research progresses, more and more gut hormones will probably be implicated in various digestive diseases and perhaps offer clues as to how to treat those diseases more effectively than they are being treated today.

Meanwhile, an analog of one gut hormone looks promising as an anti-obesity drug, reports Gerard P. Smith of New York Hospital-Cornell Medical Center in White Plains, N.Y. In 1937, a gut hormone called interogastrone was found to inhibit food intake in animals. The results were confirmed 30 years later with more pure extracts. The pancreatic hormone glucagon was also found to exert such effects. Why do these hormones cut appetite? Because food releases them from the digestive track into the circulation, they may be satiety signals. In any event, they signaled Smith and his colleague James Gibbs that they might, if injected as pharmaceuticals, turn out to be effective anti-obesity drugs.

So Smith and Gibbs started injecting various gut hormones into experimental animals, and as Smith reported at the Miles symposium, the one that works best, in either its natural or synthetic analog state, is cholecystokinin (CCK). CCK is normally made in the small intestine and acts on the gall bladder and pancreas. But higher concentrations of CCK are found in the brain than in the intestine, so CCK may have a central nervous system role in controlling behavior such as food intake. In fact, Rosalyn Yalow of the Bronx, N.Y., Veterans Administration Hospital has found that CCK is much less prevalent in the brains of a strain of genetically obese mice than in the brains of normal mice (SN: 1/27/79, p. 57). When Smith and Gibbs injected a CCK analog into hungry dogs, the animals quickly lost their appetites and stopped eating. When the researchers injected the analog into hungry monkeys, they, too, rapidly lost their appetites. And there were no toxic side effects. This past year, the investigators also found that the analog could cut appetite in hungry volunteers. Currently they are attempting to see whether the analog can also reduce appetite in moderately obese men and women.

If the CCK analog once again produces the desired effects, it may eventually receive the U.S. Food and Drug Administration's approval as an effective and safe anti-obesity drug. And if so, it would be the first one to become commercially available, since current anti-obesity treatments, such as liquid protein diets, amphetamines and intestinal bypass surgery, tend to produce more undesirable side effects than they do weight loss. □



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*Dockray: Similarities to classic hormones.*

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