



BRIEFING PAPER SERIES / *Research & Scholarship*

Knowing When to Eat, and When to Stop

FEATURED FACULTY

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MOST EVERYONE CAN AGREE that a human brain is an awesome organ. With our brain we see, hear, smell, taste and touch our world. Within the circuitry of our brain, language is born, allowing us to communicate with each other and make meaning of our lives.

But while the brain grabs all the headlines, scientists in Washington State University's Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology are making a fascinating case that the gastrointestinal tract is equally awesome and complex. We've long been told "we are what we eat," but the phrase takes on new meaning when you realize the GI tract has as many neurons as the spinal cord and secretes more hormones than any other organ system in the body. The brain may be the control center, but the GI tract is the engine.

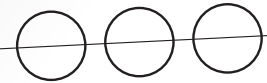
For much of our evolutionary history, and even today in many parts of the world, life was organized around getting enough to eat: growing, trading or finding enough fuel to keep our body and brain functioning well enough to go out and get more fuel. Since early humans couldn't reliably predict where their next meal was coming from, or when, it seems unlikely that our biology would be wired to prevent us from starting a meal when the opportunity arose. More likely, we are biologically wired to stop eating when we reach some predetermined threshold.

But what is that threshold and how does our body know when we've reached it? What role might sensitization to foods play in our starting and stopping consumption? With more than 34 million Americans struggling with obesity, and at risk to die from its associated health risks, WSU faculty are looking at the problem from a variety of perspectives. W. Sue Ritter's research, of particular importance to our understanding of diabetes, focuses on how the brain and gastrointestinal tract work together to compel people to eat. Her husband, Robert C. Ritter, conducts research into how the gastrointestinal tract and the brain signal a person to stop eating. Frances K. McSweeney's research in the Department of Psychology adds another element to the equation, proposing that along with hunger and satiety, another factor in eating behavior is sensitization.

THE CONTROLLING GRASP OF BIOLOGY

Every minute of our lives, our heart is beating to pump blood through our veins. Both a delivery system of nutrients and a filter of cellular waste products, our circulatory system is a marvel of checks and balances that, in a healthy person, achieve homeostasis. Cells, particularly our brain cells, have access to what they need when they need it.

In her 30-year career at WSU, **W. Sue Ritter**, a professor in the department of Veterinary and Comparative Anatomy, Pharmacology and Physiology, has been fascinated by, as she says, "the controlling grasp of biological need on brain function." With a doctorate in physiological psychology, she has focused on the brain's absolute need for glucose and the way in which the body detects that need and then mobilizes a multi-system response.



The brain's need for glucose is paramount. While the rest of our body can use alternative energy sources such as fat or protein, only glucose, a form of carbohydrate, can pass through the blood-brain barrier and fuel the trillions of neurons that are firing every moment. Adding to the difficulty is the fact that the brain cannot store glucose and so it needs a constant, steady supply.

"Because the brain has an absolute requirement for glucose as a metabolic substrate, glucose deficit is acutely life-threatening," Ritter said. In most cases, people suffering glucose deficit, or low blood sugar, benefit from an early warning system of sorts. The body not only stimulates appetite, but causes stored glycogen in the liver to be converted back to glucose and alerts the central nervous system to the physical stress the body is experiencing.

However, that early warning system often fails the people who need it most—people with diabetes on intensive insulin therapy. While people on intensive insulin therapy usually can sense a hypoglycemic episode coming on the first time it happens, subsequent episodes can result in immediate catastrophic consequences including coma or even death. Figuring out how and why Hypoglycemia-Associated Autonomic Failure (HAFF) occurs is a central concern of Ritter's lab.

With more than 16 million people suffering from diabetes in the United States, Ritter's research is of tremendous importance. That's why it is funded by both the American Diabetes Association and the Juvenile Diabetes Research Foundation.

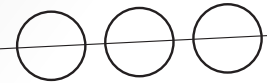
Ritter and her research colleagues, including Thu Dinh, have determined that the glucoreceptor cells are located in the hindbrain, the home of some of the brain's most primitive and basic functions. That means the glucose-sensitive cells have direct access to the body's main neural pathways and can have an immediate and comprehensive impact on the body's response. According to Ritter, the glucose control system is pervasive and powerful, causing other biological functions (such as the reproductive system) to shut down in an effort to direct all available glucose to the brain. In addition to their work on Hypoglycemic-Associated Autonomic Failure, Ritter and her colleagues are working to better understand the mechanism by which chronic glucose deficit can cause the suppression of estrus cycling.

Ritter's work is also relevant in the study of appetite and body weight regulation. With obesity drawing ever-greater attention as a wide-ranging health risk, scientists have refocused efforts on ways we can better understand appetite control. Ritter's work has shown the high priority the brain places on maintaining available glucose stores. That biologically-driven need for glucose can drive the perceived need for food intake, a fact doctors must consider when seeking effective strategies to control body weight.

Ritter earned her doctorate from Bryn Mawr College in Pennsylvania in 1973 and her bachelor's degree in psychology from Valparaiso University. Her work has been published in numerous journals including the *Journal of Comparative Neurology*, *Diabetes*, *Physiological Behavior*, *Endocrinology*, and *Brain Research*.

HOW MUCH IS ENOUGH AND HOW DO WE KNOW?

Robert C. Ritter, a professor of physiology and neuroscience, says the belief that our stomach "tells" us when we are full seems to predate our earliest written history, but scientists only began examining the role of the gastrointestinal tract in determining satiety in the past few decades. Ritter's research, which began at WSU in 1974, has been and continues to be at the forefront of figuring out what information our



gastrointestinal tract collects, how that information is communicated to the brain and what the brain does with the information once it gets it. It's an extraordinarily complicated question, but it's at the heart of myriad health risks, most obviously obesity.

Despite our popular belief that we stop eating when we "feel" full, Ritter says research shows physical feelings of fullness or satiety is an adjunct, not a trigger, for ending a meal. For instance, rats with an impaired or destroyed ability to process the sensory perception of "fullness" do, nevertheless, terminate their consumption. Instead, Ritter says, evidence suggests our gastrointestinal tract sends satiety signals to our brain, providing detailed information not only about how much is being consumed, but what is being consumed and when to stop eating. How much of the relevant information actually reaches conscious awareness is still uncertain.

Ritter says information is collected along the length of the GI tract, from the stomach to the small and large intestines, with different information collected in different areas. For instance, it appears that nerves in the small intestine monitor food calories so precisely that they can signal satiety even before the food is digested and the nutrients are absorbed into the body. The question then becomes, if the body has such a finely tuned mechanism for keeping track of calories, to the degree that many people can live their adult lives within 10 or 20 pounds of their "best" weight without ever consciously counting calories, why are so many people overweight?

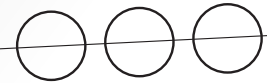
One answer, and the one that Ritter has been researching for five years, is high-fat diets. Research and anecdotal evidence agree that fat—heavy sauces, marbled meat, chocolate cream pie—cause people to feel "full" more quickly. But, further research is showing that if a person eats a high-fat diet over an extended period of time, fat can lose its effectiveness as a satiety signal. Researchers believe that dietary fat causes the nerves along the intestine to become less sensitive to the hormone cholecystokinin (CCK) which signals satiety. Since fat calories comprise nearly 50 percent of an average American diet, learning more about the role of fat in signaling satiety is extremely important. Interestingly, research has shown that even on a high-fat diet, laboratory animals are able to control their caloric intake appropriately if they are also eating a high-fiber diet. However, if the animals are fed a low-fiber, high-fat diet, they become obese.

Ritter and his colleagues are also examining the relationship between CCK and the recently discovered hormone leptin. Leptin is produced and secreted by fat cells and the more fat cells a person has, the higher the level of leptin in the bloodstream. As leptin levels rise, people with lean or average body weight generally experience reduced appetite and increased metabolism, perhaps the body's way of maintaining a consistent weight. But, among people who are seriously overweight and obese, higher levels of leptin do not appear to affect appetite or metabolism. Again, Ritter is attempting to understand why that reduced sensitivity to leptin occurs among people who are obese.

Ritter's lab is continuing to look at how the body responds to fat and other dietary nutrients, and is particularly interested in the chemical signature, or the precise molecular structure, of the nerve cells in the GI tract that are activated by fat, leptin and CCK.

Ritter's funding through the National Institutes of Health has been continuous since the 1970s. He earned his B.A. at Valparaiso University in Indiana, a V.M.D. in veterinary medicine and a Ph.D. in biology from the University of Pennsylvania.

His research has been published in more than 75 publications such as *American Journal of Physiology*, *Journal of the Autonomic Nervous System*, *Endocrinology*, and *Physiology and Behavior*.



A NEW MODEL FOR UNDERSTANDING HUMAN BEHAVIOR

When you're asked why you stopped doing something, you probably give a different explanation for different behaviors. I stopped eating because I was full. I stopped running because I was tired. I stopped playing a video game because I was bored. But **Frances K. McSweeney**, a psychology professor at WSU, has discovered one single theory she believes—and research is proving—plays an important role in determining what you do and how long you do it.

Her theory is built on the phenomenon of sensitization and habituation, which has long been recognized, and extensively studied, for arbitrary stimuli such as noise, lights and odor. Technically, habituation refers to a decrease in responsiveness to a stimulus when that stimulus is presented repeatedly or for a prolonged time. For example, when you enter a room with a noxious odor, you will be annoyed by the odor initially, but gradually, over time, the odor loses its ability to jar your sense of smell. Someone entering the room would still react, but the person already in the room would be habituated. McSweeney was one of the first to recognize that humans also habituate to biologically important substances such as food or water.

According to McSweeney, eating, drinking, exercising and other voluntary behaviors each contain a reward or reinforcer that encourages you to engage in the behavior. For example, food serves as a reinforcer for eating. However, once you habituate to the sensory properties of that reinforcer, or become accustomed to the taste, smell or texture of the food, it loses its ability to motivate and sustain your (eating) behavior. You've probably noticed that the first seven or eight spoonfuls of ice cream are usually much more appealing and satisfying than the last two or three. That's habituation.

If she is right about habituation and voluntary behaviors, McSweeney's ideas could suggest new treatment methods for a whole host of addictive behaviors, from alcoholism to drug abuse to overeating to aggression. It may help explain why one person's moderate, life-sustaining behavior becomes another person's life-threatening addiction. Determining how to hasten habituation for problem behaviors (such as overeating or alcoholism) and slow habituation for beneficial behaviors (such as exercising) could be a critical component of public health campaigns.

For example, the traditional approach to controlling obesity focuses on increasing exercise and decreasing calories. But, the idea that slow or weak habituation to food contributes to obesity suggests other approaches. Sensitization could be decreased by avoiding snacks, because "tastes" or nibbles actually increase your desire for more food. Then, by eating a less varied diet and avoiding stimulating distractions such as bright lights, loud noises, television or even conversation, a person could increase his habituation to food at mealtime, and so eat less.

McSweeney, who received WSU's 2004 Eminent Faculty Award, the highest faculty honor bestowed by the university, has been supported by grants from many agencies including the National Science Foundation and the National Institute of Mental Health. She has been at WSU since 1974 and is currently the vice provost for faculty affairs. She is a former recipient of the Edward R. Meyer Distinguished Professor of Psychology, the 2002 Sahlin Faculty Excellence Award for Research and she delivered the 1995 Distinguished Faculty address. McSweeney earned her bachelor's degree from Smith College and her doctorate from Harvard University.