NEWS

# The Dynamic Gut

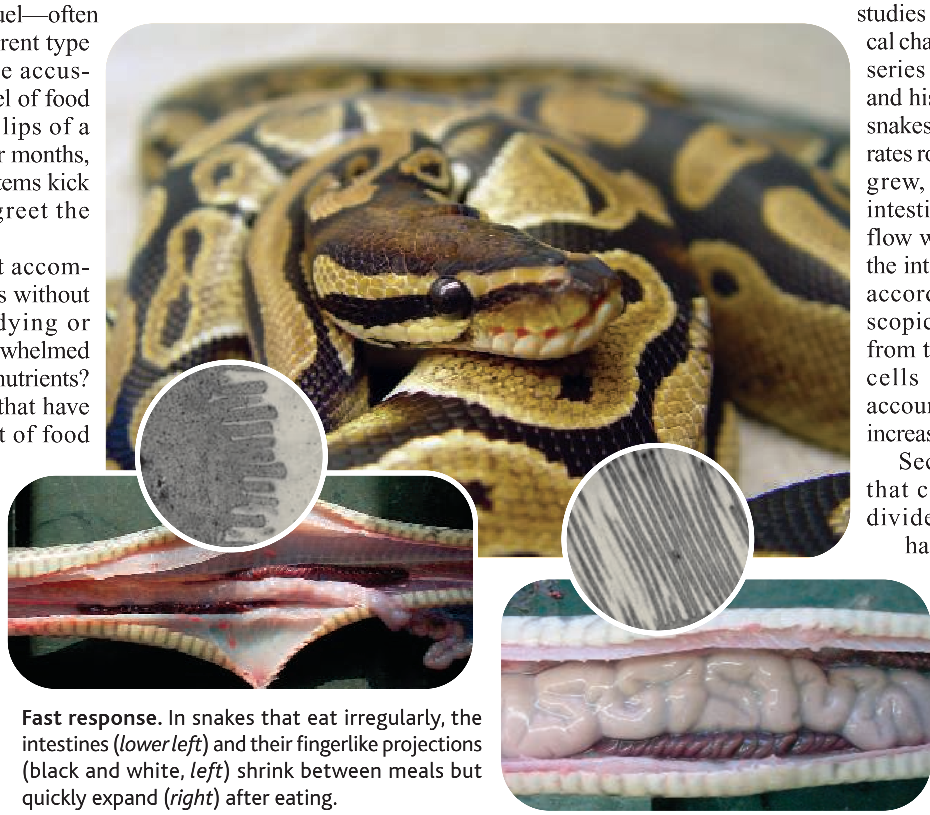
**As snakes, frogs, birds, and other wild creatures attest, digestive systems need flexibility to meet energy demands as well as the challenges of environment, diet, and predators**

You haven't had a meal for so long that your stomach and intestines have atrophied. And when you finally do get something to eat, it's almost as big as you are. Yet you cram it into your mouth and hope that your gut can somehow cope with it. That's what life's like for many snakes: feast or famine.

Other animals ride similar nutritional roller coasters. Birds travel thousands of kilometers without eating, then gorge themselves when they stop to refuel—often on a completely different type of food than they are accustomed to. Not a morsel of food or liquid passes the lips of a hibernating animal for months, yet their digestive systems kick in as soon as they greet the world again.

How does the gut accommodate such extremes without shriveling up and dying or being completely overwhelmed by a sudden flood of nutrients? Those are questions that have given biologists a lot of food for thought.

"Most of us learned in our textbooks about a rather static digestive system," says William Karasov, a physiological ecologist at the University of Wisconsin, Madison. But "the gut is a very dynamic organ." It can "adjust to changing demands and energy supply," adds Matthias Starck, a functional morphologist at the University of Munich, Germany. And those adjustments can be radical in the extreme.



**Fast response.** In snakes that eat irregularly, the intestines (*lower left*) and their fingerlike projections (black and white, *left*) shrink between meals but quickly expand (*right*) after eating.

CREDITS (TOP AND MIDDLE RIGHT ): MATTHIAS STARCK; (MIDDLE LEFT AND BOTTOM LEFT AND RIGHT) STEPHEN SECOR

### The guts of a python's survival

Among those intrigued by the gustatory habits of snakes are Jared Diamond, a physiologist at the University of California, Los Angeles, and Stephen Secor, a physiologist now at the University of Alabama, Tuscaloosa. In 1995, they reported that during the months between meals, the python's stomach and intestine atrophy. Yet once the snake begins to eat, it quickly revs up its digestive function. Secor and Diamond's work suggested that the first food to reach the gut—particularly proteins or their amino acids—stimulates a dramatic expansion of the gut lining. The intestine doubles in size, significantly increasing its absorptive surface area.

Over the past decade, Secor, Starck, and, more recently, Jean Hervé Lignot of the Louis Pasteur University/CEPE-CNRS in Strasbourg, France, have worked independently and collaboratively to sort out how this gastrointestinal rebirth occurs with every meal. The gut lining consists of "fingers" of cells called villi, and the cells themselves sport projections called microvilli. Secor's initial research indicated that new cells are added to the gut lining when the intestine shifts into high gear. That shift, especially the rapid reactivation of the stomach and the production of stomach acids, is quite energy-intensive, taxing the body's reserves, he says.

Over the past 5 years, Starck has developed an alternative explanation, one he will detail in an upcoming issue of the *Journal of Experimental Biology*. He finds that the gut lining grows not because the number of cells increases but because blood pours into shrunken villi once a snake eats, expanding the surface area of the villi and flooding them with materials needed to digest the incoming meal. According to Starck, this proposed mechanism requires less energy than Secor's original explanation; digestion can begin even when fat reserves are relatively low, he notes. And once digestion starts, the ingested food provides the energy needed to complete it.

Starck's new proposal draws on ultrasound measurements of blood flow to and within the gut lining, as well as histological studies that characterize physical changes in the lining. In one series of experiments, Starck and his colleagues fed mice to snakes. The snakes' metabolic rates rose, their small intestines grew, and blood flow to the intestines tripled. This blood flow was responsible for half the intestine's increase in size, according to Starck. Microscopic globs of fat absorbed from the gut further bloat the cells lining the intestine, accounting for the rest of the increase, he says.

Secor too has now found that cells swell rather than divide, but he thinks blood has little to do with their expansion. Instead, his work indicates that the lining's villi absorb the digestive fluids from the gut itself. Working with Secor, Lignot has used electron microscopy to show that each cell's microvilli also swell significantly, quadrupling in size within 24 hours.

Even though Secor maintains that increased blood flow is not the secret to the rapid growth of a snake gut, he has shown that it is important to digestion. Animals typically divert blood to the gut during digestion, just as exercise results in increased circulation to muscles. Last year, Secor and his colleagues reported that snakes go to extremes, increasing blood flow to the gut by about 10-fold compared to the 50% increase humans experience during digestion. "[It's] really going through the roof," Secor notes. "The cardiac output is comparable to somebody going full-



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## What's Eating You?

Sometimes, it's who's digesting you that determines how you digest. In general, long guts absorb more food and make digestion more efficient. But having a big belly, so to speak, can slow an organism down—and that's bad news in a world of predators.

Demonstrating a link between a creature's gut size and its enemies, Rick Relyea of the University of Pittsburgh in Pennsylvania and his graduate student Josh Auld have raised wood frog tadpoles under different conditions. They've set up tanks with all the ingredients of the tadpole's natural pond environment. In some, they put just tadpoles, anywhere from 20 to 160 per tank. In others, the researchers added a predator: immature dragonflies. These insects were kept in underwater cages, so the tadpoles were safe, but the dragonfly smell signaled danger. In the first experiment, which lasted a month, Auld removed 10 tadpoles from each tank several times, measured their sizes, and preserved the specimens. He later dissected the preserved specimens and measured gut lengths.

In the September 2004 *Ecology Letters*, Relyea and Auld reported that the greater the competition for food—such as in tanks with 160 tadpoles—the longer the tadpoles' guts grew. In crowded conditions, if a tadpole is lucky enough to find food, it needs to extract as much energy as possible, notes Relyea. "A great way to increase [digestive] efficiency is to have longer intestines because it forces the food to spend more time traveling through [them]," he explains—the slow journey provides more opportunities for the gut lining to absorb nutrients.

In the tanks with the caged dragonflies, however, the fear-provoking chemical cues emitted by the insect stunted gut growth. This makes sense, says Relyea. In the wild, tadpoles use their tails to dart away from dragonfly larvae, and the longer the tail, the better. But growing a long tail puts demands on the tadpole's resources, and gut length is sacrificed.

The shorter gut may be poorer at processing food, but in dragonfly-infested waters, the tradeoff for a swifter escape is likely worth it. "Animals can be amazingly sophisticated at fine-tuning their gut length to strike an effective balance between the two opposing forces of predation and competition," Relyea concludes.

**–E.P.**

**Big tail.** When these tadpoles live among predators, they sacrifice gut size for larger tails (*right*) and faster escapes.

**Au naturel.** Tanks that simulate the wood frog tadpole's natural environment enable University of Pittsburgh graduate student Nancy Schoeppner to study how predation and competition affect its gut size.

out in exercise." And the python can sustain this additional blood flow for days—plenty of time for its intestinal muscles to work without fatigue at breaking down the skin, bones, and underlying tissue of its prey.

It takes a lot of heart to pump all that blood. Indeed, the snake's heart actually grows once it eats, increasing 40% in mass in just 2 days, James Hicks, a comparative physiologist at the University of California, Irvine, and his colleagues reported in the 3 March issue of *Nature*. Athletes' hearts can also expand—but that growth happens over years, says Secor.

### Ready reserves

Even as they digest their food, snakes stockpile resources for their next great feast, says Lignot. In pythons, the stomach operates for 4 to 6 days, then begins to wind down, while the intestines keep going for at least another week to finish the job. Lignot's latest experiments show that as the intestine takes these extra days to process nutrients, it generates and banks cells for a subsequent supper. "This is the key adaptive factor: a dormant gut with unused cells that can quickly restart functioning when food is available again," says Lignot.

A similar phenomenon occurs in fasting rats. Even as they are reduced to breaking down their body's proteins—a desperate measure that can cause organs to waste away—their intestine begins to produce new cells, and programmed cell death in the lining stops, Lignot and his colleagues reported last year. "After a prolonged fast, the intestinal lining prepares itself for eventual refeeding," says Lignot.

Other animals faced with widely spaced meals have also adapted their guts to keep some cells in their digestive system up and running during the lean times. Perhaps the most extreme examples are creatures that hibernate during the cold winter or their summer counterparts that burrow and become dormant to escape life-threatening heat or dryness, a strategy called estivation. For example, Rebecca Cramp and Craig Franklin of the University of Queensland in Brisbane, Australia, have investigated the guts of green-striped burrowing frogs, an Australian species whose estivation can last more than 10 months. Once it rains hard, the frogs surface—sometimes for just a week—and they must quickly stock up on food to help find mates and build up fat reserves. Cramp and Franklin collected frogs in the wild, then allowed them to estivate in mud trays for up to 9 months. Within 3 months, the animals lost as much as 70% of their gut mass, the researchers found, and an additional 10% had disappeared by

**On duty.** While hibernating (bottom), 13-lined ground squirrels maintain minimal function in their guts but efficient digestive capacity.

CREDITS (TOP): RICK RELYEA; (BOTTOM) HANNAH CAREY/UNIVERSITY OF WISCONSIN SCHOOL OF VETERINARY MEDICINE


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9 months. The microvilli on cells of the frogs' intestinal lining also shrank.

Overall, this gastrointestinal atrophy saves energy for the frogs, explains Cramp. Nonetheless the gut of an estivating creature can still absorb nutrients, even though maintaining that readiness entails "a significant energetic cost" at a time when the frog has little energy to spare, says Cramp. But the cost is a worthwhile investment, she has discovered. Her tests have shown that frogs surfacing from estivation absorb nutrients 40% more efficiently than frogs that hadn't burrowed. Newly aroused frogs "can maximize their digestive capability from the outset," says Cramp.

Hibernating mammals called 13-lined ground squirrels also keep digestive capacity in reserve. To save energy as they hibernate, the animals' gut lining atrophies, and their intestines thin. Some cells undergo programmed cell death in response to fasting. But tissue damage is minimal as genes that promote survival and curtail cell death become active at the same time, says Hannah Carey, a physiologist at the University of Wisconsin School of Veterinary Medicine in Madison. She has taken a close look at the remaining cells and found that microvilli remain intact on the surviving cells, and their density on each cell sometimes increases. In these microvilli, transporter proteins and digestive enzymes continue to be plentiful. Thus, during brief moments when the animals come out of their stupor during those quiet months, they can absorb nutrients still left in the gut.

Indeed, when Carey warmed intestinal tissue from hibernating animals so that it could function normally, she observed that, gram for gram, the tissue worked more efficiently than did the intestines of the nonhibernating squirrels. "This is likely a beneficial adaptation," she suggests: Squirrels emerging from hibernation could make the most of spring's low food supply and still have enough energy for breeding.

**Food-flight dilemma.** Because they have different refueling strategies, red knots (*above*) have shrunken guts when they migrate, but western sandpipers (*inset*) do not.

**Always on standby.** Australia's green-striped burrowing frog keeps a few gut cells up and running in preparation for a feeding frenzy when it surfaces.

**Meals on the fly**

Like hibernation, migration places unusual demands on the gut. Migrating birds, for example, devote extraordinary amounts of energy to flying, and they must be able to digest the different foods they encounter along the way. For many migrating birds, "the way to cope with season-to-season differences in food quality and energy expenditure is to change gut size," says Theunis Piersma, an evolutionary biologist with the Royal Netherlands Institute for Sea Research on the island of Texel and the University of Groningen.

Piersma studies the red knot, a bird species that migrates between Antarctica and Northeastern Canada and Greenland. He recently showed that its gut can adjust to different diets. Red knots typically eat two types of food: relatively soft stuff such as shrimp, crabs, or spiders, and hard stuff—cockles, mussels, and other bivalves. The red knot's gizzard, the muscular extra stomach used to crunch shells, grows quickly when the bird switches from soft food to hard food, Piersma reported last year.

He and his colleagues first measured the gizzards of red knots fed trout chow for several years. They then began serving small mussels to the birds. Over the next 3 weeks, the gizzards grew by 4.9 grams; the red knots only weighed about 130 grams total. Overall, the birds gained 7.3 grams. The dietary changes experienced by migrating birds "have apparently favored the evolution of intestinal plasticity," says Rick Relyea of the University of Pittsburgh, Pennsylvania.

Piersma and his colleagues then used ultrasound to see what happens to a red knot's gut during migration. They found that when the birds arrive at a stopover, their guts are much reduced. Less intestinal baggage apparently gives the birds a better shot at making it to their destination. Yet Piersma's group has documented that when red knots make a pit stop along the Wadden Sea, their digestive systems quickly regain their ability to process food and absorb nutrients, albeit temporarily.

His team's observations show that the speed at which the gut comes back online is critical to the birds' ability to replenish the fat reserves they need to complete their journey. According to some physiologists, that ability should be limited by how fast the birds can catch their prey. But Piersma's studies show that the gut's ability to process food is the limiting step, and that their food choice—and therefore their rate of consumption—is in large part dictated by the size of their gizzards. The faster gizzards can bulk up, the greater the birds' range of food choices. "There are incredibly strong interactions between the type of food and type of digestive machinery," Piersma points out.

He and his colleagues have looked at food choices of red knots at the Wadden Sea stopover. The researchers set up patches of food along the mudflats that differed in food quality. One had many good-sized mollusks, which are relatively tough to digest. The other had a sparse smattering of crabs, which are easier for the gizzard to process but gram for gram pack less nutritional value than the mollusks. They watched as radio-tagged birds foraged in these patches and used ultrasound to measure their gizzards.

CREDITS: (TOP) CHRIS KELLY; (INSET) TOM MIDDLETON/PACIFIC WILDLIFE FOUNDATION; (BOTTOM) ED MEYER

Red knots with large gizzards, which could digest the shelled food faster, favored the larger bivalves. Those with small gizzards—the majority of the migrating birds when they first arrived—had to forage almost exclusively in the other patch. As a result, they needed to spend more time—and wasted precious energy—looking for meals. Thus, the gizzard's size seems to drive the food choice and foraging strategy of the migrating red knot, Piersma and his colleagues reported in the January *Journal of Animal Ecology*, and only if the gizzard grows fast enough will the migrants be able to lay in the stores they need for the final leg of their trip. Says Starck: "[Red knots] that optimize gut size and function arrive with more energy reserves in their breeding grounds and thus [have an] advantage over others."

In contrast to red knots, having a big gut seems to be the secret to success for some migrating birds. Consider Western Sandpipers, which migrate from Central America to Alaska. These birds actually increase the size of digestive organs for migration, according to research by Tony Williams of Simon Fraser University in Burnaby, British Columbia, his graduate student R. Will Stein, and Christopher Guglielmo, now at the University of Western Ontario, Canada.

The researchers attribute the difference between red knots and sandpipers to the species' contrasting migration habits. Red knots travel very long distances, fueling up just once during a monthlong stopover. Sandpipers hop from food stop to food stop, so they don't need to be as trim as red knots to get to their destinations.

These gastrointestinal tales of famished snakes and ravenous frogs may have implications beyond explaining how animals adjust to the nutritional ups and downs of life in the wild. Maybe, researchers speculate, a key to understanding some of the digestive diseases that affect millions of people lies in the intestines of a hibernating squirrel or the stomach of a migrating bird. "Wild animals provide model systems to study regulatory physiology [of the gut] that may be of biomedical importance," says the University of Wisconsin's Karasov.

–ELIZABETH PENNISI

NEWS

# A Mouthful of Microbes

**Oral biologists are devouring new data on the composition, activity, and pathogenic potential of microbes in the mouth, the gateway to the gut**

Thanks to dentists, "open wide" has become a command to fear. A century ago, dental practitioners depended on a shot of whiskey and pliers to treat toothaches and sore gums. Today's dentists have laser drills and Novocain, but they haven't completely shed the aura of pain. In the near future, however, the tools of choice may be less scary: a DNA test followed by a chaser of "good" bacteria, for example.

Over the past 40 years, oral biologists have been taking stock of the vast microbial communities thriving on and around teeth, gums, and the tongue. It's been known for quite some time that bacteria that normally reside in the mouth can escape to other parts of the body and cause problems. There's a well-substantiated link between one oral pathogen and heart problems, for example. And last year, tests in mice lent support to the theory that a common mouth bacterium can slip into the bloodstream of pregnant women and infect their uterus and placenta, eventually causing premature births.

**Father of oral biology.** Using the recent invention of microscopes to explore the human body, Antony van Leeuwenhoek discovered the first microbes in the mouth and recorded the diversity of these organisms.

CREDIT: CORBIS

But poor oral health also causes harm directly. Three out of 10 people over 65 have lost all their teeth. In the United States, half of all adults have either gum disease or tooth decay; Americans spend more than $60 billion a year to treat tooth decay alone. Indeed, cavities are the single most common chronic disease of childhood, with a rate five times greater than that seen for the next most prevalent disease, asthma. Adding insult to injury, about one-third of the general population also suffers from halitosis, better known as bad breath.

A lot of those problems can be traced to the mouth's microbes, say oral biologists. In healthy mouths, "good" bacteria and other microbes compete with nefarious cousins and keep them in check. But if conditions change, pathogenic microbes can gang up against the beneficial species and gain control of the mouth's surfaces. Bleeding gums, cavities, and bad breath can result.

By comparing healthy mouths to unhealthy ones, researchers are now rooting out the problematic microorganisms, which include bacteria, viruses, fungi, and even archaea. In addition, efforts to sequence the genes, if not the whole genomes, of oral microbes are helping identify the villains in the mouth and how they trigger disease. "We've been able to get a better understanding of the variety and scale of the microorganisms that are present," says Richard Lamont, a microbiologist at the University of Florida, Gainesville.

The new research clearly shows that the mouth is a complex eco-system. Some microbial species are pioneers, producing proteins that serve as welcome mats to later colonizers. It's also become evident that in the mouth, microbes gang up to cause troubles. Unlike other infectious diseases, "we are looking at infections that are caused by more than one organism," says Howard Jenkinson, a molecular microbiologist at the University of Bristol in the United Kingdom.



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