DNA affect the way proteins fold into three-dimensional structures. Critical proteins must be structurally stable for an individual organism to survive; on a population level, if too many individuals die out because their proteins are unstable, a species risks extinction.

To find the limit on mutations per genome per generation, the team modeled a range of possible stabilities for proteins essential to life. Employing a diffusion equation, widely used in physics, they calculated the balance point at which too many proteins become unstable for a population to survive. The answer they came up with: six mutations per generation.

Shakhnovich notes that this absolute speed limit illustrates why organisms that have very large genomes, such as mammals, must mutate very slowly: it is far more difficult to ensure that fewer than six mutations occur in a genome with billions of potential mutation sites than in one with several thousand. In fact, he says, most organisms operate far below the theoretical speed limit because they have developed elaborate error-correction systems to *ensure* that mutations occur only rarely.

Some diseases, on the other hand, thrive by operating near the fundamental limit of mutation. Viruses, and particularly RNA viruses like HIV, have relatively high mutation rates; only by changing their proteins constantly can they evade their host's immune system. Certain bacteria speed their evolution by shutting down their error-correction systems. Cancer cells grow and spread by mutating more quickly than normal cells.

The six-mutation rule has real-world applications. Certain therapies already take advantage of such limits by drastically *boosting* mutation rates in order to kill their targets: radiation therapy to treat cancer, for example. At the same time, the low mutation rate that allows complex organisms to support large, stable genomes limits their ability to adapt quickly in response to new conditions, as a virus or bacterium would. Global warming, for instance, may pose a particular threat to those species that evolve slowly—and Shakhnovich's team is trying to understand in more detail how the need to maintain a stable genome affects the speed at which organisms can adapt to environmental change.

—COURTNEY HUMPHRIES

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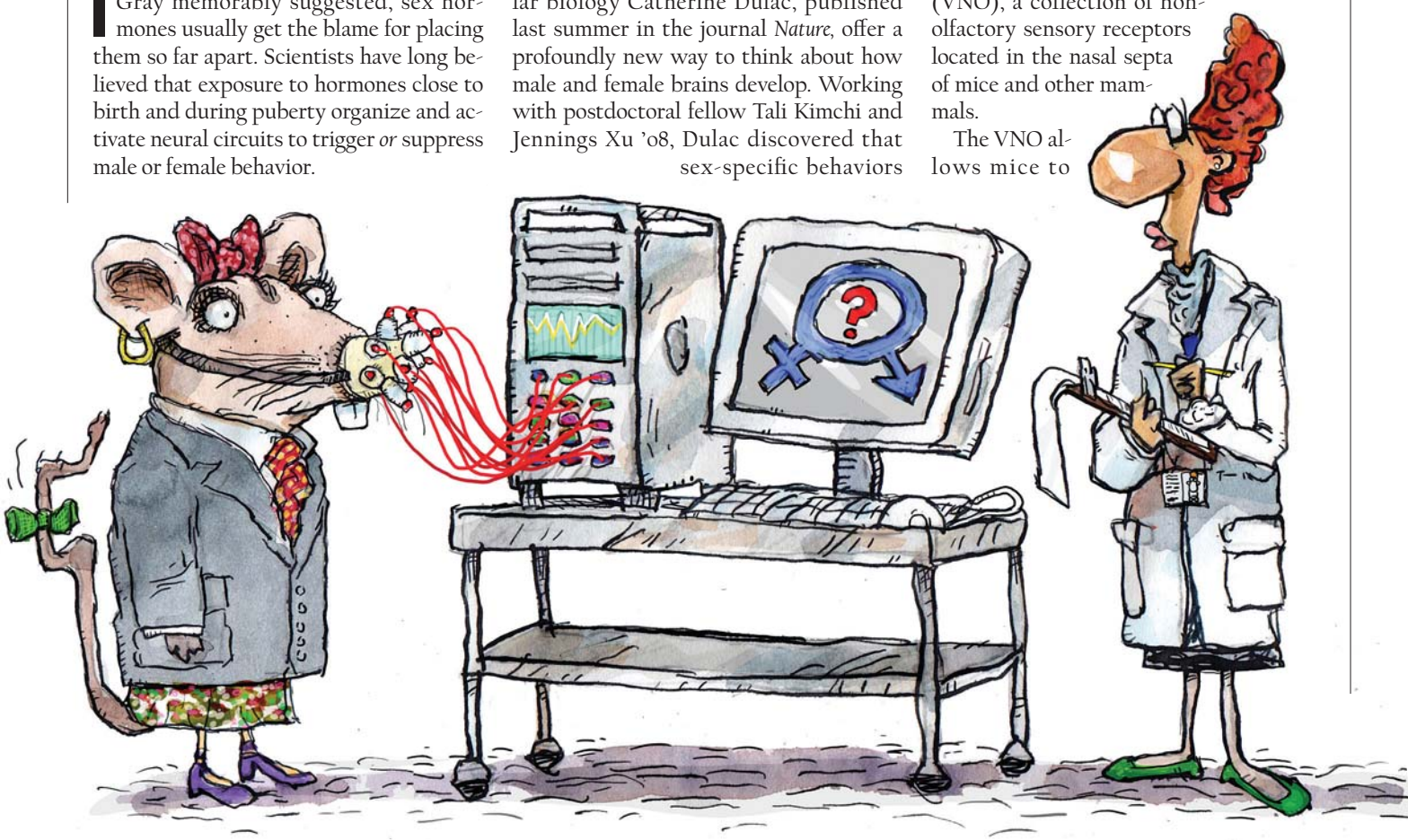
SEXUAL CIRCUITRY

When Minnie Turns Mickey

If males are from Mars and females from Venus, as self-help author John Gray memorably suggested, sex hormones usually get the blame for placing them so far apart. Scientists have long believed that exposure to hormones close to birth and during puberty organize and activate neural circuits to trigger *or* suppress male or female behavior.

But surprising findings in the lab of Higgins professor of molecular and cellular biology Catherine Dulac, published last summer in the journal *Nature*, offer a profoundly new way to think about how male and female brains develop. Working with postdoctoral fellow Tali Kimchi and Jennings Xu '08, Dulac discovered that sex-specific behaviors in mice switch on and off at the command of the vomeronasal organ (VNO), a collection of non-olfactory sensory receptors located in the nasal septa of mice and other mammals.

The VNO allows mice to



sense pheromones: chemicals that animals within a species give off to communicate "who is male, who is female, who is a pup, who is a parent, who is kin, and who is a foreigner," Dulac explains. Her lab is devoted to examining the control of instinctive behavior—particularly social actions such as aggression, maternal behavior, and courtship—within animal brains. In an effort to determine how the VNO affects behavior among female mice, Dulac and her coauthors bred "knock-out mice" lacking the TRPC2 gene, thereby deactivating the VNO.

When Dulac's coauthor Kimchi placed these female mutants in a cage with normal male mice, "what she observed was completely astonishing," Dulac says. "The females started to behave exactly like males." Suspecting an error, the puzzled researchers checked the mice to ensure that they truly were female. But there was no mistake. Though female, with normal hormone levels and estrus cycles, these mice emitted ultrasonic vocalizations normally sung by males to attract mates and, like males, they mounted their cage mates and engaged in pelvic thrusting. When impregnated by male mice, these females also lacked the usual maternal behavior. They neglected their pups shortly after birth and failed to attack intruder males while nursing their young.

Dulac says the researchers wondered if the mice behaved oddly because they had grown up without a functional VNO, which altered their brain development. "In sensory biology," she explains, "there is an important concept known as 'critical period,' which holds that if a sensory modality is not used during early development, it won't function properly, even if it is restored." She cites classic experiments conducted with kittens that were blindfolded from birth. When the masks were later removed, the kittens couldn't see properly because their brains had never developed the appropriate neural pathways to process visual information. But when Dulac's team tested this hypothesis by surgically removing VNOs from adult female mice that had developed normally, the surgically altered females still behaved just like males.

These VNO-free females led Dulac and her coauthors to craft a dramatically new hypothesis about brain development: female mouse brains, they propose, contain a fully functional circuit that produces male behavior, but the VNO serves as a switch to repress male behavior and activate female behavior. In fact, Dulac suspects that all mouse brains contain circuits for both male and female behavior, and pheromonal cues determine which circuit is activated. "From a developmental standpoint," she says, "this makes a lot of sense, because male and female have essentially the same genome, and one genome helps to build one brain." She believes this model may very well apply to other animals, including humans, but further research is needed. "Our new model has many implications," Dulac says, "and it will be exciting to conceive experiments to see how robust [it] is."

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The mouse findings don't apply directly to humans; for starters, we don't have vomeronasal organs to switch between male and female circuits—just pits where the VNO used to be. Evolution failed to preserve the organ, Dulac says, because humans rely more heavily on their eyes than their noses: roughly a third of the rodent brain is dedicated to smell and pheromone detection, where nearly a third of the human brain is devoted to sight.

This fact led Dulac to theorize that visual input in humans may play the same role as pheromones do in mice. "Humans hate to consider that they have instinctive behavior," she observes. "We see ourselves as very rational animals, completely

Illustration by Tom Mosser

in control of what we want to do." Yet humans, she adds, do have a pheromone equivalent: pornography. "It elicits sexual behavior, which is exactly what happens to a mouse smelling a pheromone," she says. "Obviously we can resist some of the stimuli; we have many layers of control for behavior. But there is something here that reminds us of the instinctive behavior in animals." —ERIN O'DONNELL

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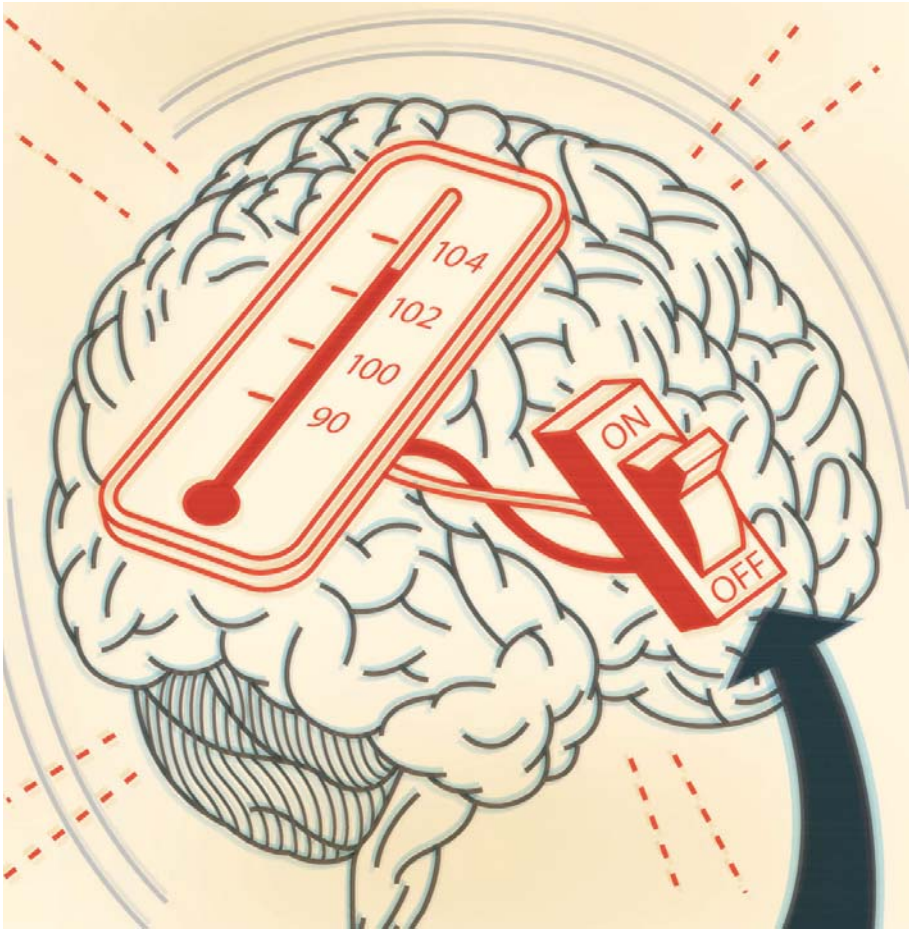

BODILY BLUNDERBUSS

"Tyrant Fever's" Trigger

When an infection assails the body, the response is predictable. Fever, loss of appetite, fatigue, that achy feeling—we never get just one without the others. Scientists believe this is because the entire suite of symptoms is governed by hormones called prostaglandins—but they also believe each individual symptom has a separate trigger site in the brain.

Now researchers at Harvard Medical School have identified the site where fever begins. Using genetically engineered mice, a team led by Putnam professor of neurology and neuroscience Clifford Saper, M.D., and postdoctoral fellow Michael Lazarus confirmed their hypothesis that the fever response originates in the brain's hypothalamus region, in a group of nerve cells two millimeters across by five long. (The Harvard team knew which type of hormone was involved because about 10 years ago, researchers in Japan had engineered mice that lacked prostaglandins throughout their bodies and found that such mice didn't develop a fever when injected with bacteria; the Harvard group sought proof that receptors in the brain, rather than somewhere else in the body, trigger fever.)

Because of the genetic manipulation involved, Saper's lab will not try to replicate the finding in humans. Rather, the next step is to find drugs that block the prostaglandin receptors linked to fever. The lab is also collaborating with researchers at the University of Tennessee to begin looking for the spot in the brain where achiness originates. Saper hopes he or others will succeed in isolating the trigger sites for all the symptoms that typically accompany fever. "It would be nice," he says, "to know how to turn off different components of this system."

For its part, the body—by responding with every weapon in its arsenal—mounts the strongest possible defense against disease, akin to fighting a land, sea, and air war all at the same time. This multipronged response succeeds against many types of adversaries; it evolved to keep us alive, but it makes us feel miserable, sometimes unnecessarily. It is impossible for the body to decouple the individual symptoms without making a major change in its response to illness. This is because those symptoms are not responses to individual stimuli; rather, they are *all* responses to the same stimulus, the presence of prostaglandins.

The direct causes of prostaglandin production are the presence of cytokines—hormone-like chemicals that the white blood cells of the immune system produce as part of the body's inflammation response—and the presence of bacterial cell-wall components that (outside a laboratory) are generally an indicator of infection. No matter what the stimulus, whether a cold, the flu, a cut, or a chronic condition such as arthritis or Crohn's disease, the body produces the same response: first inflammation, then prostaglandins, fever, aches, fatigue, and decreased appetite. This happens whenever there is systemic, as opposed to localized, inflammation.

In some cases this response may be overkill. For instance, loss of appetite—which reduces blood glucose if it causes us to eat less—may seem a wise strategy for stemming the growth of bacteria, which thrive in a sugar-rich environment. But when invaders *aren't* replicating in the bloodstream, eating a normal amount may actually *help* the body fend off illness by restoring energy reserves.

By blocking the action of one or more of the trigger sites, doctors and patients of the future could customize the body's re-

Illustration by Harry Campbell