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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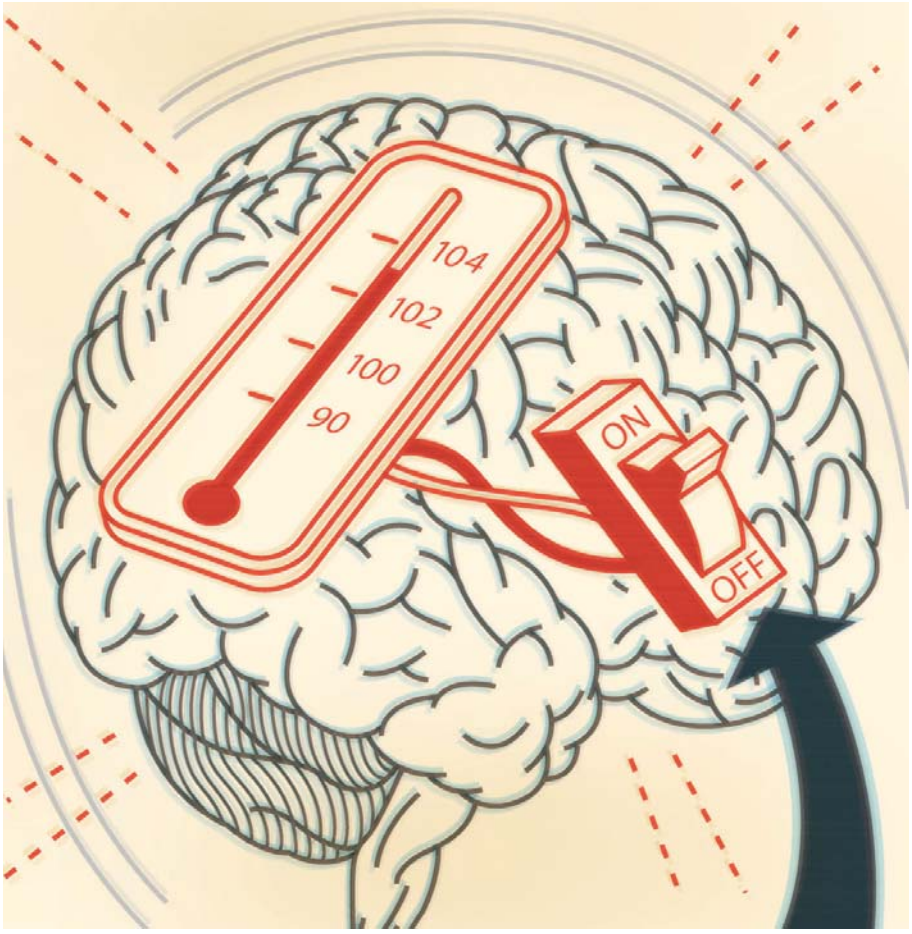

BODILY BLUNDERBUSS

"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

sponse to illness, keeping the symptoms that help and eliminating those that don't. "People with cancer, for example, are always very fatigued," says Saper. "In fact, there's a chronic fatigue syndrome that we don't understand at all, and that may be due to some mechanism that we can get a handle on by looking at what causes fatigue in inflammatory conditions."

Once those sites are identified, scientists will still have much more to learn before the targeted response Saper envisions becomes possible. Researchers understand little about how each symptom works to enhance the immune response. They know white blood cells function better at higher temperatures, but don't fully understand why; without knowing that, it's hard to say whether having a fever is helpful or harmful in treating specific ailments. The functions of achiness and fatigue are even more of a mystery: it makes intuitive sense that conserving energy lets the body marshal its resources to fight off illness, but, says Saper, "Nobody's looked at the mechanism."

Doctors and patients of the future could customize the body's response to illness, keeping the symptoms that help and eliminating those that don't.

Even without a complete understanding of the immune response, he and his team are forging ahead, seeking ways to block individual symptoms—and the chief over-the-counter antidote for fever offers an instructive model. Aspirin's naturally occurring precursor, willow bark, had already been in medicinal use for millennia before the drug itself was first synthesized, in 1897, and it wasn't until the 1970s that scientists learned *how* aspirin works: by preventing the formation of prostaglandins. Now the hunt is on for other, more targeted, medications that might be used with similar effect.

—ELIZABETH GUDRAIS

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