Like Minds
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In 2011, science threw a curveball at Nicholas Dodman, head of Cummings School's Behavior Clinic, and Alice Moon-Fanelli, another animal behaviorist, then at Tufts.

The researchers were looking at bull terriers in hopes of finding the gene responsible for a debilitating behavior common in the breed. Up to 85 percent of any litter will compulsively chase their tails, sometimes to the point of savaging themselves or anyone who tries to interrupt them.

A statistical analysis of data, including sex, medical history and other behaviors found in 145 affected bull terriers and 188 "control" pets, revealed some surprises. The vast majority of affected dogs were males, and many had other strange behaviors or physical conditions that accompanied the tail chasing, such as explosive aggression, partial seizures, phobias, skin conditions, gastrointestinal issues, object fixation and a tendency to shy away from people and other dogs.

"How could we possibly explain this?" Dodman recalls, before he realized there were similarities between these canine behaviors and autism in people. "The primary behavioral expression of autism in humans is that a child is slow to develop speech and other social behaviors," he says. "But if you weren't able to factor speech into the equation, you may still observe repetitive behaviors like spinning, rocking or flapping hands, temper outbursts and sometimes seizures. Affected bull terriers show many of these behaviors."

Indeed, when Dodman, Moon-Fanelli and researchers from the Sackler School of Graduate Biomedical Sciences at Tufts looked for biological similarities between tail-chasing bull terriers and children diagnosed with autism, they found significantly elevated levels of two biomarkers in the children and the dogs. The findings were published in *Translational Psychiatry,* October 2014.

Quelling the Skeptics

The notion that behavioral disorders in people and animals might share some commonalities has long met with skepticism in scientific circles. But Tufts researchers have helped move that concept from anthropomorphism to evidence that has led to new treatments for people and pets—including a new patent on a drug to treat obsessive-compulsive disorder in humans.

Dodman never intended to specialize in the animal mind. However, not long after he arrived at Tufts' veterinary school in 1981, he received a call from Louis Shuster, a pharmacologist at Tufts School of Medicine who was studying drug abuse.

Shuster had read a scientific paper about racehorses becoming increasingly sensitive to the stimulant effects of morphine with every dose, instead of more tolerant to the drug, as is typical in people. He had observed the same bizarre phenomenon in rodents exposed to opioids and enlisted Dodman for a study that confirmed that exposure to morphine indeed led to similar behaviors in horses.

The morphine-induced equine behaviors—endlessly pacing the stall or digging at the ground—overlapped with what equestrians call "stall vices," says Dodman. In animals, these abnormal, seemingly pointless and sometimes self-injurious behaviors are referred to as "stereotypies." Because stereotypies are common in horses kept stabled most of the time, Dodman wondered whether that might mean the horses were "self-medicating" to cope with the stress of confinement. "I thought the abnormal behavior could be due to nature's own morphine: the endorphins."

Shuster agreed, and they set out to determine whether a medication that blocks the body from responding to opioids and endorphins could rein in stall vices.

Eureka Poker

They turned to Poker's Queen Bee, a palomino mare that engaged in "cribbing," a tooth-eroding behavior in which horses clamp down on a stall door or fence, tense their neck muscles and repeatedly gulp air. Dodman and Shuster plotted the incidence of the mare's cribbing before and after she was injected, first with control doses of saline and then with the opioid-blocking drug naloxone (the Narcan now used to treat heroin overdoses).

The opioid blocker worked. "We could control the horse's behavior by controlling its brain chemistry," Dodman says. "We turned the infusion rate up, and the horse stopped cribbing. We turned it down, and it started cribbing again. It was the eureka moment that changed all our lives."

Shuster shifted his research focus from the drugs of addiction to the behaviors of addiction. And Dodman found a new calling: treating animal behavior problems.

After working with horses through the 1980s, Dodman and Shuster started studying dogs with stereotypies, particularly those with lick granulomas, a condition in which pets create an open wound by endlessly licking their leg. Again the duo found that drugs that blocked the body from responding to opioids lessened the repetitive behavior.

In 1992, Judith L. Rapoport, a psychiatrist at the National Institutes of Health (NIH), published *The Boy Who Couldn't Stop Washing: The Experience and Treatment of Obsessive-Compulsive Disorder.* "She went around the United States on a book tour, and when she got back to her office, she had all these messages from pet owners about their dogs engaging in similar behaviors," says Dodman. "Instead of pooh-poohing the idea, Rapoport did some research and found that the dogs responded to the same drugs used to treat OCD," he says. "It appeared [that] what we were calling stereotypies in animals might be more accurately called compulsive disorders."

Roughly 2 to 3 percent of people have some form of OCD, according to Dodman, who notes that animals can also suffer from a similar smorgasbord of compulsions. Border collies chase beams of light. Siamese cats won't stop sucking on fabric or plastic. African grey parrots pluck themselves bald.

As in humans, compulsive behavior in animals often seems to be driven by genetics. "If the genetic predisposition is there, these behaviors can be triggered by stress and myriad environmental factors," says Dodman.

For example, in a study soon to be published in *The Journal of Veterinary Behavior,* Stephanie Borns-Weil, V07, identified a strong association between early weaning in Birman cats, a breed with a high genetic risk for a compulsive fabric-sucking disorder, and the development of that abnormal behavior.

In both animals and people, repetitive behaviors often stem from anxiety, and engaging in them appears to bring some relief, says Dodman. But the relief is fleeting, and the OCD loop is on an endless repeat. While treatment of people with OCD usually involves cognitive behavioral therapy, pets' compulsive behavior is managed by environmental changes designed to reduce stress and a class of mood-stabilizing drugs that includes Prozac.

"It is stressful for an animal to be deprived of the opportunity to engage in its normal behavior patterns," says Borns-Weil, now a behavior resident at Cummings School. At Tufts, she and Dodman work with owners to reduce pets' stress by adding more exercise and otherwise enriching their lives to ward off anxiety caused by isolation and lack of stimulation.

Selective serotonin reuptake inhibitor (SSRI) medications, such as clomipramine and fluoxetine (Prozac), are used to treat compulsive disorders in pets and people, Borns-Weil says. "Unfortunately, as in people, these medications do not always provide meaningful improvements in a compulsive pet's quality of life," she notes.

New OCD Drug

Dodman and Shuster, now a professor emeritus, have improved these animals' lives by identifying a new OCD drug. When they studied opioid-blocking drugs in mice, dogs and horses, they realized that those same drugs also blocked NMDA receptors, which help the body process glutamate, a neurotransmitter that's important for cognition, memory and learning. When they tested drugs that block glutamate, such as dextromethorphan (found in cough medicine) or memantine (developed as an Alzheimer's drug), on compulsive behaviors in genetically engineered mice and dogs with compulsive behaviors, the mice stopped their self-scratching, and many of the dogs showed a significant reduction in their compulsive behaviors.

The two approached Michael Jenike, head of the Obsessive Compulsive Disorders Institute at McLean Hospital in Belmont, Massachusetts, who was convinced enough to try memantine on a few of his patients who did not respond to SSRIs. After the patients reported improvement in their symptoms, the three researchers conducted a study comparing 22 people with OCD receiving cognitive behavioral therapy with 22 OCD patients who also took memantine. Only the memantine- takers saw significant decreases in their OCD symptoms, according to their study, published in the *Journal of Clinical Psychopharmacology* in 2013. Tufts patented memantine as a new treatment for OCD, and psychiatrists are now using it alongside SSRIs in people with better results.

Despite those outcomes, most scientists who study human psychiatric conditions, including Jenike, will not entertain the idea of too many similarities between a behavior disorder in humans, a species that has landed on the moon, and one in dogs, a species known to sneak snacks from unguarded litterboxes. "I have a hard time with the concept of a dog biting on his leg and calling it OCD," Jenike told *Science* magazine in 2010. "With OCD, you need to know what's going on in the head. It's kind of a big leap for me."

A Simpler Route to the Genetic Roots

Nonetheless, pets—particularly purebred dogs and their very similar DNA blueprints—could play an important role in understanding which genes influence the brain and thus modify behavior in animals with compulsive tendencies.

"It's become very clear over the past decade that although we have amazing new genomic and genetic tools, it's still very difficult to find disease genes [in humans] for many neuropsychiatric disorders, particularly those associated with behavioral differences such as what we observe in autism," says Matthew Huentelman, an associate professor in the Neurogenomics Division of the Translational Genomics Research Institute (TGen) in Arizona. "So while we aren't stopping our work in human beings, working in purebred animals should dramatically simplify things for us on the genetics side. By looking in the dog genome, essentially the job of finding that disease-causing gene is made 100 times—or even 1,000 times—easier." (See "Cancer Genetics.")

Pets' inability to tell us what's wrong may even be a plus in the search for the roots of our shared behavioral disorders, says Elaine Ostrander, chief of the Comparative Genomics Branch at the NIH. While it's easy to determine whether a person has a specific type of cancer, behavioral disorders aren't always clear-cut because of other factors, such as age, medications taken, IQ and even a personal or family history of divorce, alcoholism, drug addiction or physical abuse. "All those things ultimately affect some behavioral manifestations of disease, and boy, it is really hard to develop behavioral tests that strip them all away," says Ostrander. "Now, add to that the fact that people often answer questionnaires according to how they perceive the questioner wants them to. Well, with dogs, we don't have any of these issues."

To help better understand the genetic underpinnings of compulsive disorders in pets and people,

Dodman and a team of researchers from Tufts, the Broad Institute of Harvard and MIT and the University of Massachusetts Medical School compared the genes of normal Doberman pinschers to those in the breed exhibiting compulsive disorders. Compulsive tendencies are about four times more prevalent in Dobermans than in adult humans, Dodman says, noting that up to 70 percent of pups in a litter might display such behaviors as flank-sucking.

The researchers were the first to identify a mutation in a canine behavior gene: CDH2 on chromosome 7. (This gene for a protein called neural cadherin is on chromosome 18 in humans, the so-called "psychiatric chromosome.") CDH2 is responsible for the formation of neurons, synapses and NMDA receptors, which receive glutamate, the same neurotransmitter blocked by the Tufts- patented OCD drug. The study appeared in *Molecular Psychiatry* in 2010.

Earlier this year, Dodman led another genetics study involving Dobermans, this one examining pets that were unaffected, mildly affected or severely affected by compulsive flank-sucking. The study found that although the CDH2 gene on chromosome 7 puts dogs at risk of developing this behavior, a second serotonin-receptor gene on chromosome 34 influences the severity of the disorder.

"It's no coincidence that we've gone fishing in these dogs' genetic pool and picked out an NMDA and a serotonin gene—both related to the two OCD treatments that work for people and dogs," says Dodman. He says he's even more excited about a Chinese study published in *PLOS One* in October 2014 about the genetic root of compulsive circling, a behavior common in the Belgian Malinois, a working dog that is very similar to German shepherds, a breed also known to circle compulsively. "They found the same gene that we found in Dobermans—CDH2. We now have two completely different expressions of OCD in two completely different breeds with the same genetic causation," he says. "From these findings we hope to investigate the pathways involved, and that may lead to new treatments."

A Test for Autism

Now Dodman is using the animal model he started with—tail-chasing bull terriers—to investigate the genetics of autism.

He has teamed again with Huentelman and Ostrander, along with Edward Ginns from the University of Massachusetts Medical School. They hope the Canines, Kids and Autism Study, funded by the American Humane Association, will produce a genetic test for autism, which affects 1 in 68 children, according to the Centers for Disease Control and Prevention.

With such a tool, physicians could "hopefully identify kids who are at the highest risk for autism earlier than we have ever done before," says Huentelman. "Research shows that the earlier you start behavioral therapy, the better outcome those interventions have in terms of lessening the severity of the symptoms of autism spectrum disorder."