

# THE HAPPINESS PROJECT

## Advocates are pushing to enrich the lives of rodents and fish in the lab, but critics worry about the impact on research

*By* **David Grimm**, *in Ann Arbor, Michigan*

PHOTO: AUSTIN THOMASON/MICHIGAN PHOTOGRAPHY

A mouse at the University of Michigan in Ann Arbor is transferred from cage to cage in a tube, rather than being hoisted by its tail—a common, but stressful maneuver.

If they weren't in the windowless basement of a cavernous biomedical research building, the "Aquatic Suites" might sound like a cushy vacation destination. But the zebrafish here at the University of Michigan (UM) still have it pretty good. In a large room full of aquaria, the striped, pinkie-size swimmers flit past fake green plants, white plastic tunnels, and multicolored marbles that may remind them of the bottoms of lakes and streams. These simple accoutrements are a luxury for creatures typically housed with little more than food and the water they swim in. And the enrichments may make the animals better at what they do: serving as important models for human disease.

For decades, lab animals such as rodents and fish have lived in barren enclosures: a small plastic box, few—if any—companions, and little else. The smaller the number of variables, the thinking went, the greater the accuracy of the experiment. But a growing number of studies suggests that this approach may have backfired. Only one in nine drugs that works in animals ever succeeds in human clinical trials, and labs often struggle to reproduce one another's results. Could the environment these creatures live in be part of the problem?

That's what a new group of advocates argues. "We're trying to control these animals so much, they're no longer useful," says Joseph Garner, a behavioral scientist who runs a program to improve the value and welfare of lab animals at Stanford University in Palo Alto, California. "If we want animals to tell us about stuff that's going to happen in people, we need to treat them more like people."

Garner and others are pushing scientists to enrich the lives of the creatures in their care by giving them toys, companions, and opportunities to exercise and explore—in short, a life more like they would have in the wild. These proponents are driven by both a concern for the welfare of lab animals and a desire to make their contributions to research more meaningful. And they're beginning to conduct experiments that show that such enrichments not only benefit animals, but science as well.

However, other researchers fear that adding extras to animal cages could muddy experiments and exacerbate the reproducibility crisis. And given the tens of millions of rodents and fish in U.S. labs alone, they blanch at the cost. "There's nothing natural about what we're doing, and adding a few tubes to a cage is not going to change that," says Jonathan Godbout, a neuroscientist at The Ohio State University (OSU) in Columbus who studies aging and stress in mice. "The more we spend on this stuff, the less research we can do."

**LABORATORY ANIMALS** didn't always live such a barren lifestyle. Researchers began breeding rats for scientific experiments in the mid-1800s, and early cages allowed the rodents to burrow and run on wheels. But by the 1960s, in an effort to standardize care and limit variables, labs began to prioritize small, cheap, and sterile enclosures. There was little regard for the animals' natural habits, as long as they were free of obvious pain and suffering. The goal, in essence, was to create furry test tubes.

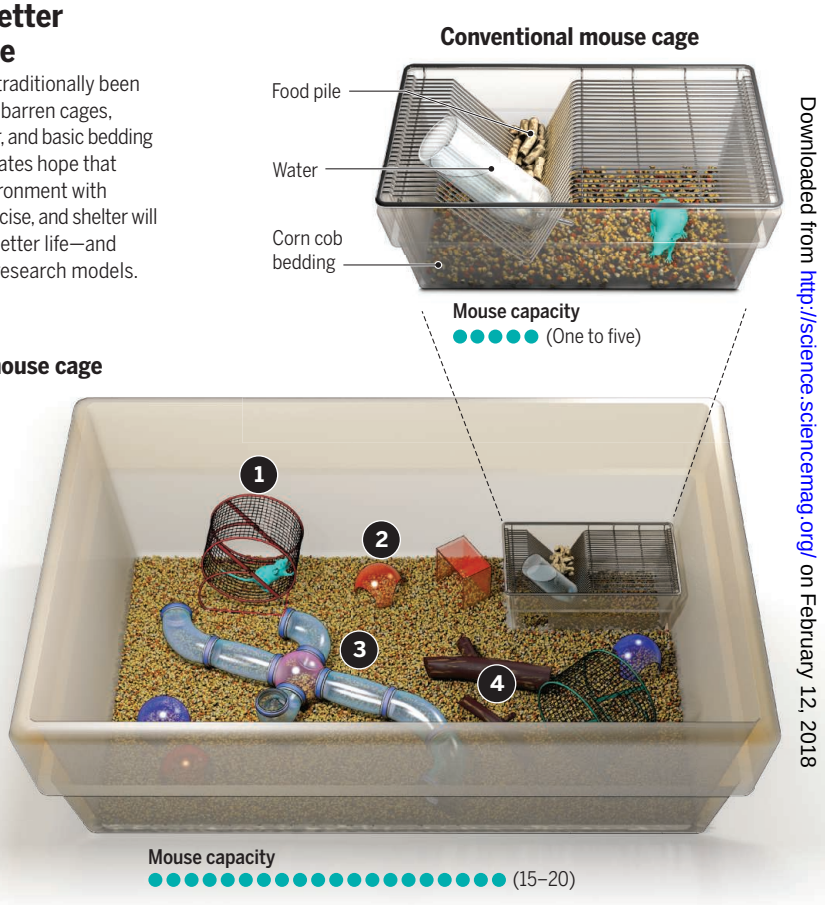
Today, lab mice live in shoebox-size cages hundreds of thousands of times smaller than their natural ranges, and rats can't forage or even stand upright. Both spend their days blasted by ventilation and bright fluorescent lighting that disrupts their day-night cycles. "We're doing the exact opposite of what we should be doing to make these animals happy," Garner says. Lab animals tend to be obese, have weak immune systems, and develop cancer—all before scientists do any experiments on them.

The first hints that enrichment could help came in the 1940s. In 1947, psychologist Donald Hebb found that rats he raised with his daughters and gave free rein in his home were better learners than lab-raised rodents. In the 1960s, researchers showed that lab rats provided with wooden blocks and a rotating assortment of mazes developed larger sensory regions of their brains.

Yet the only enclosures that changed were those of nonhuman primates. Amendments to the U.S. Animal Welfare Act in 1985 required labs to promote the psychological well-being of the monkeys and chimpanzees in their care, giving them more space, toys, and comrades. The U.S. National Research Council's 1996 *Guide for the Care and Use of Laboratory Animals* went further, prompting animal care staff to add perches, blankets to make nests, and even music and movies. But rodents and fish were largely ignored.

## Building a better mouse house

Mice and rats have traditionally been housed in relatively barren cages, with only food, water, and basic bedding material. But advocates hope that enriching their environment with objects for play, exercise, and shelter will give the animals a better life—and make them better research models.




GRAPHIC: V. ALTOUNIAN/*SCIENCE*

Then, in 2000, neuroscientist Anthony Hannan at the University of Melbourne in Australia decided to spice up the lives of his lab mice. Inspired by research that showed enrichment could spark the growth of new neurons, he provided the rodents with cardboard for making nests, brightly colored balls for play, and ladders and ropes to climb. Remarkably, the animals were much slower to develop symptoms of a Huntington-like disease than their counterparts in standard housing—the first demonstration that enrichment could significantly influence neurological disorders.

"Before we did this work, everyone thought Huntington's was 100% genetic," says Hannan, whose team has gone on to show similar results in rodent models of autism, depression, and Alzheimer's disease.

In the past decade, a growing body of work has suggested that rodents and other animals have complex mental lives and can experience a range of emotions once only attributed to people. Scientists have learned more about the power of enrichment, too. In 2010, cancer biologist Lei Cao—inspired by a family member who had died of cancer—wondered whether she could combat it by looking beyond drugs or genes. Her team at OSU created a 1-square-meter enclosure filled with so many mazes, running wheels, and bright red, blue, and orange igloos that her daughter dubbed it "Disneyland for Mice."

When injected with cancer cells, animals housed there developed tumors 80% smaller than those in control mice, or no tumors at all. Cao even discovered a possible mechanism: A stimulating environment seemed to activate the brain's hypothalamus, which regulates hormones that affect everything from mood to cancer proliferation. "We showed that there's a hard science behind enrichment," she says. "You can't just treat the body—you have to treat the mind."

Such findings fit with what we know about how we ourselves respond to our environment. Stress, depression, and lack of social support can boost the risk of cancer in people, and less active individuals are more likely to develop diseases like Huntington later in life.

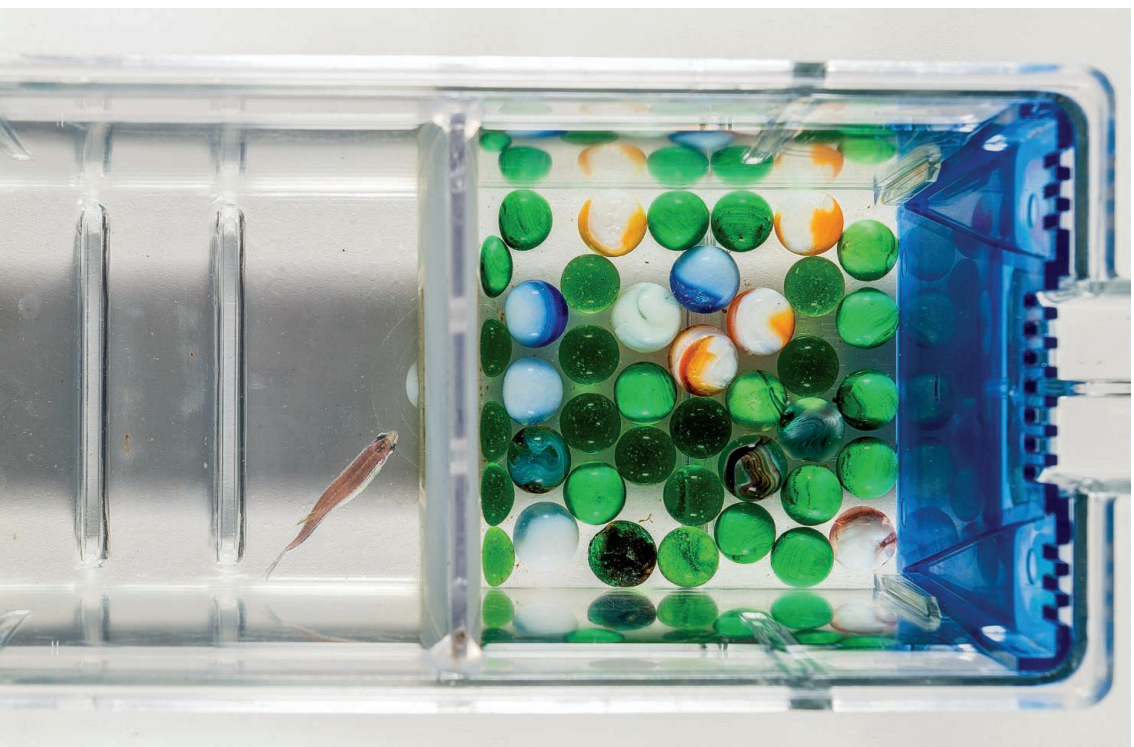
In the past few years, a host of other studies has demonstrated the power of enrichment. Giving rodents and other animals toys, exercise, and companions appears to reduce their susceptibility to epilepsy, multiple sclerosis, and addiction. Research published last year showed that enrichment helps mice fight infections and sharpens rats' memories.

The growing literature inspired the National Research Council to update its guide in 2011. Like similar guidelines in Europe, it states that all naturally social species should be socially housed if possible, and advocates enrichment for all lab animals, not just nonhuman primates.

Yet scientists can avoid these guidelines if they successfully argue that enrichment will compromise their studies, and universities vary in how they apply enrichment. Showing that enrichment produces happier, healthier lab animals is, after all, not the same as demonstrating that it yields better science. Some researchers want more evidence that enrichment boosts the quality of experimental results.

"My mind could be changed by good science," Godbout says. "If someone comes out with clear-cut data that enrichment impacts the kind of work we do, then of course we'd follow it."

That's what efforts like the fish experiment at UM are trying to provide.



A fish at the University of Michigan in Ann Arbor gets to choose between an empty tank and one filled with marbles.

PHOTO: AUSTIN THOMASON/MICHIGAN PHOTOGRAPHY

**BACK IN THE AQUATIC SUITES**, veterinarian Jennifer Lofgren is peering into a zebrafish tank. There's a transparent plastic divider in the middle, with a hole to swim through. On one side is an enrichment—multicolored marbles lining the bottom—while the other side is empty. The idea is to see where fish spend more time, and thus which enrichment, if any, they prefer. "We can't just throw random objects like treasure chests in there because we think it looks cool," Lofgren says. "We want to put some science behind it."

That's the goal of the university's Refinement & Enrichment Advancements Laboratory (REAL), an unusual program Lofgren co-founded in 2014. REAL's team of vets and animal care technicians aims to "understand the lived experience of the animal," she says, and to nurture what it has evolved to do. The marbles, for example, might reduce the fish's anxiety by making the tank feel a bit more like the wild. (They're also easier to clean than gravel.)

Stress can affect a wide range of physiologies and behaviors, and researchers are beginning to test whether the additions make the animals better models for depression—and, in the case of these particular fish—retinal regeneration. "If we provide subpar welfare," Lofgren says, "we are also providing subpar science."

Across campus, she and her team are also trying to improve the lives of rabbits. In a fancy, heavily glassed building once owned by biotech giant Pfizer sits a room filled with 50 white bunnies in metal cages the size of large laundry baskets.

Most are housed alone, as has been the standard for decades.

"The going theory is that you can't socially house rabbits, because they'll tear each other apart," says Lofgren, even though the animals live in teeming warrens in the wild. For the past few years, her group has been getting some animals to share cages by providing enrichment: hay-filled paper bags they can "forage" through, plastic keys to gnaw on, and other accoutrements. "Now, they're playing together and snuggling up with each other," she says.

Once they've firmed up the enrichments, Lofgren and colleagues will explore how they affect research results. These animals are used in studies of cardiovascular disease, and isolated rabbits sometimes have irregular circadian rhythms, which can influence heart rate, blood pressure, and hormone levels. "We want to study the impact of diet and drugs on atherosclerosis, not the impact of these other variables," says Patrick Lester, the vet in charge of the rabbits. "If we can eliminate them, we can create a cleaner signal."

The bunnies don't appreciate every addition, and there's an easy way to tell. "They'll pee on it, and shove it into a corner," Lofgren says. Enrichments that the animals like are added to a database that REAL shares across campus and with other labs, including those in the United States that house some 150,000 rabbits. Lofgren says a recent webinar on their rabbit work attracted 90 institutions. "They get back in touch and say, 'Oh my gosh, it actually worked!'"

Other labs are forging their own paths. At the University of Minho in Braga, Portugal, animal facility manager Magda João Castelhano Carlos has helped develop PhenoWorld, a sort of McMansion for rats with exercise rooms fitted with running wheels, dining areas with food and water, and experimental spaces with levers for cognition testing. The rodents must learn how to open the tunnels that lead to each room, giving them daily challenges. The animals engage in more natural play behavior, Carlos says, and are better models for psychiatric disorders because they're not unnaturally depressed or anxious.

Similarly, some rats at the University of British Columbia in Vancouver, Canada, can stand, climb ladders, and burrow in real soil in four-level cages created by biologist Daniel Weary and postdoc Joanna Makowska. "Our dream," Weary says, "is that our animals live a better life with us than if they had never been born."

Despite the boon to animals, some worry that when it comes to research, such enrichments could do more harm than good.

**A CASE IN POINT** is a strategy pioneered by Lofgren's group to ease a major trauma in the life of a lab mouse. Imagine a giant reaching into your house every week, hoisting you up by your legs, and plopping you into a new home. That's what the lab mice in a room stacked with nearly 900 cages on UM's medical campus deal with every time staff pick them up to clean their enclosures. "It's one of the most stressful things you can do to them," Lofgren says.

To ease that stress, her group adds plastic tubes to some cages. The goal is to get the rodents accustomed to the tubes and to spending time in them. Then, when cleaning time comes, the animal care staff wait for the mice to enter the tubes (or gently nudge them in), and transfer the whole shebang to a new enclosure. If it works, Lofgren says her team will apply the practice across campus.

But there's no free lunch here: With 49,000 mouse cages at the university, the kinder, gentler cleaning would add considerable expense. The 49,000 tubes would have to be sterilized, and cleaning each cage could take up to 10 times longer.

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Such numbers concern some scientists, including Godbout. "If you're paying $1 per cage now, and then suddenly it's $2 per cage, how do you afford that," he asks, "especially when our budgets are not keeping pace?"

Godbout and others also worry that far from improving research, enrichment could compromise it. If a lab is studying the impact of stress on the growth of new neurons, for example, and then it lets mice exercise on a running wheel—which has been shown to spark neuron growth—the study could be jeopardized, Godbout says. And if every lab uses a different enrichment, it could complicate the ability to reproduce another lab's experiments, and thus add to, not fix, the reproducibility crisis.

What's more, says John Crabbe, a behavioral geneticist at the Portland Veterans Affairs Medical Center in Oregon who researches alcoholism in mice, just because an enrichment works for one type of disorder doesn't mean it should be applied to all. "If you show it works in tumor studies, I have no trouble with it being the guideline for tumor studies," he says. "But don't generalize it to psychiatric disease."

Godbout says he's all for giving lab animals the best life possible, but he argues that—in a world where they get as much food as they want and don't have to worry about being eaten by predators—they're already living a good life. "You don't need an amusement park to keep them happy."

Hannan acknowledges that enrichment can make studies more expensive. But he argues that the strategy would lead to better studies more likely to translate to human health, saving time and money in the long run. "Less research could be done," he says, "but it would be better research."

Persuading the doubters will take time, in part because money for studies is scarce. The National Institutes of Health in Bethesda, Maryland, doesn't support enrichment research because it doesn't directly relate to the health and well-being of humans, says Patricia Brown, director of the agency's Office of Laboratory Animal Welfare. "We would if we could," she says. "A happy mouse is a better model."

The REAL program gets the vast share of its financing from UM funds designed to improve animal care and use, and a few small organizations offer grants for such work. Hannan's seminal Huntington study came out of his own pocket. "We never could have gotten a grant to do it," he says, "so we just did it."

Still, the chorus for enrichment is growing. "More and more, people are reaching out to us," Lofgren says. "We're starting to see some real momentum." More than 160 papers were published on rodent enrichment in 2016 versus a handful at the turn of the millennium; at the 2016 meeting of the American Association for Laboratory Animal Science, 83 out of 171 rodent presentations focused on enrichment—more than twice the number at the 2009 meeting.

Meanwhile, REAL continues to explore what makes animals happy. Lofgren plans to line the walls of UM's sheep runs with photos of contented sheep, for example, because studies suggest that the animals recognize each others' faces. She and her fellow enrichment advocates hope that one day, work like this will be become the rule, rather than the exception, both for the sake of science and for the animals themselves. "We owe it to these creatures to give them the best lives possible," Lofgren says. "They're giving us the best they can. So we should be doing the best we can." ■

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*Science* **359** (6376), 624-627.
DOI: 10.1126/science.359.6376.624