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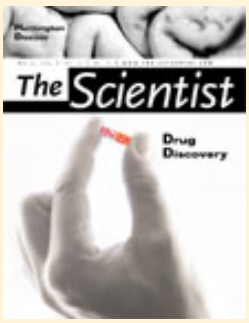

Feature

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Creature Comforts

Housing animals in complex environments where they must use motor and thinking skills alters research results | By Hal Cohen

All Illustrations: Tammy Irvine, Rear View Illustrations

Researchers are bringing the wild inside their laboratories. Compelled by studies that suggest animals' bodies and minds react to even minor changes in living conditions, scientists are decorating animal cage interiors to mimic the exterior world of nature, thus challenging lab animals to think and move.

A large, complex living space outfitted with objects that stimulate animals' mental and physical growth form the ideals of environmental enrichment (EE)--a field of study started by psychologists in the 1960s, which has now moved mainstream, particularly among neuroscientists. Advocates of EE say that providing multifaceted living conditions is

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essential to the mental and physical well-being of lab animals and could also influence the validity of experimental results. "You can argue whether your previous results are valid or not," says Vera Baumans, professor of laboratory animal science at the Karolinska Institute in Stockholm. "At KI we're going to find out if that is the case."

Not all labs take enrichment as seriously as the Karolinska Institute, but the growing interest in the relationship between environment and experimental results has converged with the influence of animal rights' groups on science policy, so that labs are becoming more aware than ever of animal care. "Effects from differential experiences have been found in species from fly to philosopher," says Mark Rosenzweig, professor emeritus of graduate studies at the University of California, Berkeley, and pioneer of applying environmental enrichment to laboratory testing. "Many investigators have come to realize that animals raised without sufficient stimulation do not develop full growth of brain or full behavioral capacities."

Emma Hockly, research fellow at Guy's Hospital, Kings College London, has found that even minimal enrichment, consisting of a plastic tunnel for running and food on the cage floor, for example, slows the development of symptoms of Huntington disease (HD) in mice.[1] Creating a higher level of enrichment, by using a running wheel, tunnels, toys, gnawing sticks, and extra bedding, has helped stave off the decline of motor performance and further slow the advancement of HD. "There's kind of a rapid degeneration but there is still a marked improvement," in motor skills, Hockly says. The improvements are due to the cognitive and physical stimuli provided by an enriched environment: Animals with nothing to do in a life of captivity may turn to self-mutilating activities, says Elizabeth Gould, neuroscientist and

professor at Princeton University, who works with primates.

INVENTING ENRICHMENT Psychologist Donald Hebb pioneered the field of environmental enrichment in the 1940s by raising rats in his home. Hebb found that his home provided a more challenging environment than that supplied through standard laboratory conditions, and the rats responded by displaying enhanced intelligence and superior problem solving skills.

In the early 1960s, a group led by Rosenzweig was using environmental enrichment when the team inadvertently challenged the long-held theory that the adult animal brain cannot show changes in volume as a result of learning or experience. Using rats housed 12 to a cage with stimulating objects, Rosenzweig compared learning ability to differences in brain chemistry. The rats housed in an enriched environment had increased activity of acetylcholinesterase (the enzyme that initiates the synaptic transmitter, acetylcholine), but Rosenzweig also found unexpected changes in cortical morphology: an 8% increase in thickness of the cerebral cortex, and an increased number of neurons and synapses. "We found that the cerebral cortex could vary with experience, something that had never before been demonstrated," Rozenzweig says.[2]

When neuroanatomist Marian C. Diamond joined the Rosenzweig group in 1961, the team found that these differential experiences in environment were also producing detailed changes in neuroanatomy, including alterations in neuron size, numbers of synaptic contacts, and

branches of the dendritic tree.

This breakthrough led to subsequent discoveries by Bill Greenough, professor of psychology and psychiatry at the University of Illinois at Urbana-Champaign, who demonstrated that brain plasticity was not limited to neurons. He found that within the capillary system, the carrying capacity per neuron increased by nearly 100%. "Synapses were principally increased by learning, and vasculature capillaries were increased by activity, suggesting that different elements respond differently," Greenough explains.

UPDATING ENRICHMENT Because Rosenzweig's group challenged the dogma that adult brain measures were set and could not be increased, members of the biomedical community scoffed at such a startling discovery made by psychologists. "Our findings weren't new or important until a prominent scientist said that 'everyone already knew' that the brain is highly plastic," Rosenzweig says. Nevertheless, Rosenzweig's legacy lives on as environmental enrichment in experimentation continues at a pace even he says he couldn't have envisioned.

At Princeton, Gould has applied enriched living conditions in several of her studies of nonhuman primates. The cages in Gould's lab are 64 times the size mandated by the NIH for nonhuman primates, big enough for Gould to stand in, which is more representative of their natural home. The environment

THE LAW ON ANIMAL CARE

The Animal Welfare Act (AWA), America's foremost animal protection law, covers some lab animals, such as primates, dogs, and guinea pigs. But in 1972, the US Department of Agriculture declared that mice, rats, and birds were exempt from AWA protections. An updated version of the AWA, enacted in 1985, bolsters the standards of care for all laboratory animals, and specifically promotes "the psychological well-being of primates." Though an estimated 25 million lab rats and mice are still exempt from AWA,[1] most major US research institutions receive money from the Public Health Service, and must have their animal welfare guidelines approved by the National Institutes of Health Office for Laboratory Animal Welfare.

In Europe, the "Convention For The Protection Of Vertebrate Animals Used For

inside the cage is changed every other day, using different toys and live vegetation to recreate the natural environment of a rainforest. Tree branches with drilled holes allow the monkeys to forage for insects and fruit. "It's very expensive and very labor intensive to recreate environments," Gould says "but the animals are getting many more cognitive challenges interacting with the environment than the animals who just hang on the walls doing nothing."

Experimental And Other Scientific Purposes" provides guidelines for creating lab environments that allow some freedom of movement, as well as supply of food, water, and care appropriate to animals' health and well-being. The guidelines, which must be ratified, also state that researchers should check environmental conditions daily and monitor the animals' emotional well-being.

1. D. Malakoff, "The rise of the mouse, biomedicine's model mammal," *Science*, 288:248-53, 2000.

The stimuli and pressures that come from living in an environment where animals socially interact and apply critical thinking in their daily routine, to find their meals, for example, are a crucial part of brain development. The enrichment has contributed to many of Gould's findings. In an enriched colony of marmosets, Gould saw changed parameters in every brain region, and in adult rhesus macaques, she observed increased neurogenesis in the dentate gyrus, and newly generated cells in the hippocampus.[3]

Gould says that environmental enrichment helps prevent stresses that can inhibit neurogenesis. "We know that if we manipulate small experiences in their lives, we can get fairly large changes in the brain," she says. "Simply put, animals living in deprivation don't make for a good control group."

Gould's lab, a veritable country club compared to the bare-bones environs of food and bedding lab animals often receive, demonstrates the importance of the interaction between the social and physical environment, although which aspect has a greater impact remains debatable. "In some ways it's like asking if height or width contributes more greatly to the area of a rectangle," Greenough says. Providing social partners appears to be the most significant input for reducing behavioral abnormalities. Yoland Smith, professor of neurology at Yerkes National Primate Research Center in Atlanta, keeps his monkeys

housed singularly in large cages, allowing him to control variables such as food intake. But the cages are close enough that the animals can communicate.

COSTS OF COMPASSION Scientists such as Smith and Gould increasingly show the benefits of improving the social and physical environments for lab animals, the higher costs and the possibility of diminished standardization among experiments are contentious issues. Researchers may desire to provide the best facilities for their test subjects, but larger enclosures take up more real estate in the lab, and they raise the per diem costs of caring for the animals. Big cages also require a budget for furnishings, as a monkey with nothing to do in a larger cage isn't likely to show any change in behavior. Toys must be purchased frequently, as nonhuman primates, much like their human counterparts, become bored easily.

Some labs have done everything but hold bake sales to maintain favorable conditions. Gould's lab members and those in other departments often put in extra hours so that specialized staff need not be hired. In addition to cost, the use of lab space and toys to enrich the environment creates difficulties with standardization among labs. Encouraging animals to forage, nest, and play presents new experimental variables to be controlled. "Researchers try to create environments consistent between labs, but small changes in enrichment can have big effects," Hockly says. "It's so difficult to be sure that you're doing the same thing as other labs. You just have to make sure to be consistent in your own lab."

Baumans' work suggests that subtle differences in enrichment protocols can affect animals' responses to surgery, making standardization of those protocols significant. Baumans observed a difference between test groups living in the minimal environment of a small cage with the slight enrichment of sawdust, and those in an environment enriched with nesting material, a climbing grid, gnawing sticks, and a plastic tube.

"When you look at the physiology, the enriched and nonenriched will differ," Baumans says. "An animal in an environmental enrichment [program] will show more species-specific behavior because they can do more. They will be better learners." But, Baumans adds, researchers can aim for only relative standardization, as animals themselves may show differences before they even get to the lab. "We know that animals from different suppliers will also differ," Bauman says, "so you're getting completely different animals to begin with. People have said that enrichment increases variation, but an animal is not a test tube. There will always be variations."

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2. D. Kretch et al., "Relations between brain chemistry and problem-solving among rats raised in enriched and impoverished environments," *J Comp* Physiol Psychol, 55:801-7, 1962.

3. E. Gould, C.G. Gross, "Neurogenesis in adult mammals: Some progress and problems," *J Neurosci*, 22:619-23, 2002.

THE WELL-APPOINTED ANIMAL HOUSE

Some researchers complain that the words "enriched environment" have become buzzwords, and it would seem that way: The phrase can cover a range of inputs, including not only cages that permit greater range of movement and more natural activities (www.cages-bh.com), but even fruit-flavored wood blocks (www.ottoenvironmental.com).

The short explanation is that enriched environment refers to a blend of better places to live, more animal-animal interaction, and more activities. The trend has spawned a whole industry, with vendors competing to provide "enrichment devices." It all leaves many researchers wondering whether primates or rodents will actually like any of that stuff in the catalogs. (Some people even advocate for enrichment for invertebrates, so don't think you're off the hook just because you work on *Aplysia* or locusts.)

John P. Capitanio, professor of psychology and associate director for research and development, California National Primate Research Center at the University of California, Davis, warns that whatever object you are considering, you should avoid the temptation to anthropomorphize. Just because you love the Dilbert chew-toy doesn't mean your lab animal will, too.

In enriched environments, food itself becomes a toy. Through the use of foraging devices, food should be hidden and challenging to access, as it is in the wild. Foraging devices run the gamut from commercially made plastic puzzle balls in unnatural colors to bamboo hollowed out by lab members. Kristen Anderson, manager of the primate lab at UC-Davis, says the animals don't balk at neon-colored plastics. However, since primates have color vision, she suggests that researchers consider the possible implications of an object's color on the outcome of certain experiments. She also warns that researchers must use species-specific foraging devices.

Another consideration, says Anderson, is the age of the animals. Older animals may lack both the manual dexterity and the healthy teeth necessary to use foraging devices successfully. And, especially when dealing with primates, the animal's personality can affect outcome. The same object that delights one animal may frighten or bore another, not unlike journal papers.

When commercial products prove too expensive or inappropriate, researchers can often have their own custom devices made in university shops or by local craftspeople. Another choice is to buy an off-the-shelf device and have it modified. Anderson says her facility buys regular balls and splits them open to make extremely simple puzzle balls.

One of the cheapest and most readily available sources can be a local pet store, or better still, if your lab is in an agricultural area, a feed store. In all cases, says Anderson, you must test a new device or toy, first by having lab members do whatever they can to destroy it, then by giving it to one of the strongest animals. If it survives, then it should be safe to give to the rest of the colony.

--Karen Heyman

THE ENRICHED EXPERIMENT

William Greenough's often-repeated admonition is that an enriched environment for a laboratory animal is really just a closer approximation to a normal environment. Greenough, professor of psychology and psychiatry at the University of Illinois at Urbana- Champaign, says all the hype about enriched environments comes down to something obvious: If you give a plant water and fertilizer, it blooms.

Elizabeth Gould, neuroscientist and professor at Princeton University, wonders whether enrichment is simply reversing a deprivation effect. "I've never seen anyone show the difference between complex environments and super-complex environments," she says. In other words, what happens when you give a plant extra water and fertilizer? Would it do better? Or worse? Those experiments with animals still need to be done.

Scientists can be led astray when enrichment is used as a catch-all term, according to Judy Cameron, associate scientist at the Oregon National Primate Research Center. "'Enrichment' makes a judgment call on what is good and what is bad," she says. "I bend over backwards not to use the word. Enriching to whom? To you? To the animal? What species of animal? USDA inspectors tell me to give my monkeys TV, but certain species of monkeys don't like TV." It would be more accurate to describe what it is you are actually working on, adds Cameron. "If you're talking about the effects of enrichment on the brain," she adds, "then you're really talking about plasticity."

At its worst, the supposition that enrichment is good and nonenrichment is bad can lead scientists to question the value of experiments done under deprived (nonenriched) conditions: Should decades of earlier research be thrown out? The answer, according to several researchers, depends on the nature of the topic studied. Says Gould, "The environment may not matter for certain basic questions about sensory processing; however, for learning and memory it could be quite different." The issue of adult neurogensis was not even taken seriously until animals were placed in an enriched environment, she adds. In essence, says John Capitanio, an associate director at the California National Primate Research Center at University of California, Davis, a photo receptor is a photo receptor; it's not going to change, simply because an animal now has a foraging device.

Cameron agrees. "You first have to ask, 'Does the enriched environment change behavior,'" she says, "And then as a result does it change biochemical pathways?" She's concerned that no one has yet quantified how much time animals spend with enrichment devices, a task she has assigned to Kristen Coleman,

her former postdoctoral trainee, now an assistant scientist at the Oregon Primate Research Center. "Many toys given to animals don't get played with at all," Cameron says.

All researchers are concerned that once environmental effects are taken into account, experimental variables increase drastically, including things beyond control such as unexpected construction noise, power failures, or animals simply not liking each other. "You start to consider really fundamental questions about the scientific method itself," Capitanio says. Cameron and Capitanio both point out that researchers doing behavioral studies need to pay more attention to the entire life histories of their lab animals, not just where were they raised, but how many and what kind of experiments they have already been through. Researchers are beginning to include information on their animals' past environments in methodology sections, says Cameron, though few include histories. Since older studies often do not include any of this information, it is difficult to judge whether they should be invalidated.

For those inclined to argue that all older studies are now worthless, Capitanio poses this: "In twenty years, when we'll have discovered some way to [remotely record brain signals], will we be saying, 'Look at all those fMRI studies, the animals were stressed and anesthetized. How valid can any of those results be?'"

Finally, consider this: Just how natural is an enriched environment in which the predator experience is missing? Cameron has been excoriated by People for the Ethical Treatment of Animals (PETA) and the popular news media for her experiments in which gliders are flown over a primate colony. Her work tests neurochemical correlates of anxiety, and the gliders are a close approximation of a true stressor for a wild monkey: a circling raptor.

--Karen Heyman

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