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Laboratory Rodent Welfare: Thinking Outside the Cage

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ABSTRACT

This commentary presents the case against housing rats and mice in laboratory cages; the commentary bases its case on their sentience, natural history, and the varied detriments of laboratory conditions. The commentary gives 5 arguments to support this position: (a) rats and mice have a high degree of sentience and can suffer, (b) laboratory environments cause suffering, (c) rats and mice in the wild have discrete behavioral needs, (d) rats and mice bred for many generations in the laboratory retain these needs, and (e) these needs are not met in laboratory cages.

INTRODUCTION

Rodents have an unenviable place in science. House mice, *Mus musculus* (hereafter mice), and Norway rats, *Rattus norvegicus* (hereafter rats), rank first and second in numbers of individuals used in laboratory experiments and testing protocols. Carbone (2004) estimated that upward of 100 million mice are now consumed yearly in U.S. laboratories, owing in part to the steep rise in use of transgenic, nonhuman animals. Their collective welfare is further jeopardized by the fact that rats and mice are commonly viewed as “lower mammals” and are specifically excluded from the United States Animal Welfare Act.

In ongoing debates about animal experimentation, welfare concerns usually revolve around harms done to animals by the experiments themselves. However, there is ample evidence that “laboratory animals,” including rats and mice, suffer not just from the experimental protocols but also from their day-to-day living conditions. (“Laboratory animals” is being used here as shorthand for animals in the laboratories and should not be taken to imply anything about the animals’ nature or purpose.)

A recent review reported that routine husbandry and monitoring methods such as blood collections, oral dosing, and even moving and cleaning cages cause marked nontransient increases in the animals’ stress markers. The review concluded that these responses reflect pain, discomfort, and/or fear of an aversive event (Balcombe, Barnard, & Sandusky, 2004).

Another hardship is the animals’ housing, where lives are spent confined in small, barren cages, often in social isolation. For purposes of this article, I define “cage” functionally, as a confined space that thwarts basic natural behaviors such as exercising, exploring, foraging, and choosing social partners. These living environments prevent animals from exerting control over their situation and severely restrict strongly motivated behaviors such as

foraging, hiding, nesting, exploring, climbing, burrowing, and choosing social partners (Balcombe, 2006; Jennings et al., 1998; Latham & Mason, 2004). As a result, the animals' neurological (Kempermann, Kuhn, & Gage, 1997) and psychological (Zhu et al., 2006) health may be adversely affected, which can further compromise scientific justifications for animal use in research (Würbel, 2002). Behavioral stereotypes—repetitive, unvarying, and apparently functionless behavior patterns commonly seen in chronically confined animals—commonly arise in rodents kept in laboratories and are believed to reflect suffering (Mason, 1991).

There is a substantial amount of research on the welfare of rodents housed in laboratory cages. This body of research wholly assumes that we will and, by insinuation, that we should continue to use such housing. The focus is on exploring the case for better cages—that is, improving confinement by the addition of enrichments. Here I present arguments to support the position that the cage itself is intrinsic to the problem and that—notwithstanding the experiments themselves—noncaged conditions are the only ones that would genuinely take the rodents' interests into account.

RODENT SENTIENCE

Published research indicates that rats and mice are aware, emotional, highly sentient, and—in the case of rats at least—considerably intelligent. Rats and mice have acute olfactory, acoustic, gustatory, and somatosensory perceptions (Burn, 2008; Diamond, von Heimendahl, Knutsen, Kleinfeld, & Ahissar, 2008; Mackay-Sim & Laing, 1980; Timm, 1994). Their visual systems, although relatively poor in brighter light conditions, are highly adapted to the low-light conditions they experience in the wild.

House mice also show hallmarks of complex beings vulnerable to suffering. At least eight methods to study pain and stress are widely used on mice. These protocols elicit avoidance behaviors (Tramullas, Martínez-Cué, & Hurlé, 2008) and pain-anticipation responses (Suaudeau, do-Rego, & Costentin, 2005). A recent study demonstrated that weanling mice often produce ultrasonic vocalizations in response to painful stimuli but remain silent in sham-pain scenarios (W. O. Williams, Riskin, & Mott, 2008). Rats are also widely used as models for human pain. For example, studies of neuropathic pain in rats show long-lasting effects on behavior (Back et al., 2008), and rats show expected aversions to cold and heat (Vierck, Acosta-Rua, Rossi, & Neubert, 2008).

Awareness implies vigilance in observing or alertness in drawing inferences from what one experiences (Merriam-Webster, 2008). Rats demonstrate metacognition—that they know what they know. Rats almost always choose the correct answer in a simple discrimination task; when the discrimination becomes difficult, however, they opt to “vote” (by poking their nose into a cone) to decline the test and proceed directly to the next trial (for a small reward) rather than risk failure and no reward (Foote & Crystal, 2007). Rats can learn by observation (Laland & Plotkin, 1990) and by imitation (Heyes & Dawson, 1990), and they understand cause-and-effect (Blaisdell, Sawa, Leising, & Waldmann, 2006). As early as 1948 it was shown that rats form mental maps. When placed in familiar mazes in which optimum pathways to food had been blocked, rats quickly chose efficient new routes to their goal (Tolman, 1948).

Highly social mammals, rats have evolved behaviors that can be described as considerate or empathic. A 1959 study titled "Emotional Reactions of Rats to the Pain of Others" showed that rats would stop pressing a bar to obtain food if doing so delivered an electric shock to a rat next to them (Church, 1959). In another study, rats pressed a lever to lower to the floor a squirming, vocalizing rat trapped in a suspended harness (Rice & Gainer, 1962); they did not respond to a suspended block of Styrofoam. Perhaps the Good Samaritan rats merely wanted to stop a disturbing stimulus and were not concerned for the other rat; however, at the very least, a form of empathy termed "emotional contagion" was occurring (Preston & de Waal, 2002). Rats also show an emotional fever response, their body temperatures rising when handled by an unfamiliar person but not so if the person is known and trusted (Briese & deQuijada, 1970). Meticulous studies suggest rats' capacity for joy (Burgdorf & Panksepp, 2001) and for optimism and pessimism based on their living conditions (Harding, Paul, & Mendl, 2004).

Mice are well attuned to, and aware of, their social milieus. They leave small traces of urine wherever they go, from which other mice can recognize individuals, and extract information on social status, genetic relatedness to themselves, and parasite load (Ehman & Scott, 2001; Hurst et al., 2001; Malone Payne, Beynon, & Hurst, 2001; Manning & Dawkins, 1998). When scientists at McGill University injected painful irritants into the stomachs and paws of mice, they noted the animals' "writhing" responses. By placing a mouse in a neighboring cage, it was observed that a witnessing mouse became significantly more sensitive to painful stimuli, but only if the neighbor was familiar with the writhing mouse. The authors concluded that house mice show a "primitive" form of empathy (Langford et al., 2006).

Our poor vantage point in understanding mice is illustrated by the recent discovery that the vocal repertoire of house mice includes courtship songs sung by males to females (Holy & Guo, 2005). These ultrasonic serenades are considered songs because they comprise several different syllable types, utterances of repeated phrases, and idiosyncratic syllabic and temporal structure (Holy & Guo, 2005).

NATURAL BEHAVIOR

Animals' sensory and cognitive capacities are a product of the natural environments in which they have evolved. Social and opportunistic, rats are extremely adaptable and inquisitive omnivores with catholic food tastes (Walker, 1964). Their subterranean tunnels provide shelter for raising young and protection while eating. Both sexes build nests of grass, leaves, and other soft materials. A typical home range is between 2,500 and 5,000 m² (Jackson, 1982; Stroud, 1982), though some rats have been known to travel 2–3 miles a night to forage in farmed fields at harvesttime.

Rats in the wild live in colonies. Females, usually related to each other, live in small groups of one to six in their own burrow system. A male rat might succeed in monopolizing a burrow of females. At high population density, however, males can no longer defend a burrow against intruders; the social system becomes despotic,

with one socially dominant male and several subordinates (Lott, 1984). Dispersal (both within and between colonies) is male biased, with females tending to stay in their home colonies whereas males leave to join other colonies.

House mice are extremely adaptable. Habitats include buildings, fields, croplands, river borders, and—to a lesser extent—various forest and shrub habitats. House mice forage on a wide variety of foods. These foods include grains, fruits, seeds, vegetables, fleshy roots, meat, arthropods, glue, paste, soap, and other household articles (Silver, 1995); in addition, they are very selective when there is a wide variety of foods available (Mackintosh, 1981). Wild house mice typically eat about 200 small meals nightly, returning to some 20 to 30 food sites (Meehan, 1984; Potter, 1994).

Nests are constructed in burrows or in protected spots in human-made structures or woodpiles. A female is persistent and vigorous in her nesting efforts and may make more than 150 trips to retrieve nest materials (Brown, 1953). Given the chance, she typically constructs several entrances to her nest (Brown, 1953). Although territorial (Mackintosh, 1970), the species is nevertheless gregarious, living in strongly cohesive social groups (Lidicker, 1976).

Home range varies widely, probably due to variations in forage distribution and carrying capacity. Some mice dwell in well-defined home ranges of <10 m across (Young, Strecker, & Emlen, 1950); others move constantly over much larger distances, traveling kilometers daily (Silver, 1995). Dispersal is important, particularly for males (Brown, 1953; Lidicker, 1976), and studies consistently find that adult males have significantly larger home ranges than do females (Hackmann, Wuest, & Barrett, 1980; Mikesic & Drickamer, 1992).

THE TRAVAILS OF CURRENT LABORATORY CONDITIONS

Many normal behaviors of a rat or mouse are thwarted by standard laboratory housing systems, which are based more on practical and economic considerations than on biological ones (Würbel, 2002). Housing consists of small “shoe box” cages (Olsson & Dahlborn, 2002) usually stacked in an enclosed, windowless room. Water and food in the form of dry commercial pellets are typically provided ad libitum, and sawdust is commonly the only further provision (Olsson & Dahlborn). The small size of typical laboratory cages fairly precludes opportunities to exercise or explore (Figure 1). For rats, UK and U.S. housing requirements and recommendations provide between 0.010 and 0.080 m² floor areas per animal and minimum cage height of 18 cm. Mice are typically provided between 0.004 and 0.020 m² floor area per animal and cage height of 12 cm. These standards largely reflect current practice (Balcombe, 2006).

Caging imposes restrictions on normal social dynamics in rodents (Latham & Mason, 2004). Solitary housing of rats and mice remains commonplace today, especially in testing protocols (Van Loo, Van de Weerd, Van Zutphen, & Baumans, 2004; Verwer, van der Ven, van den Bos, & Hendriksen, 2007). Mice in the laboratory are typically separated from their mothers at 21 days old, even though in the wild they

would not disperse from their natal territory until around 35–42 days (Van Loo et al.; Verwer et al.). Animals in labs also have no choice in when they disperse from the natal territory (Latham & Mason, 2008). The greater complexity of natural environments allows intruders or subordinates to evade pursuits and attacks by residents. In contrast, small cages thwart opportunities for escape from aggressive encounters or from smells and sounds of potentially threatening conspecifics (Hurst, Barnard, Tolladay, Nevison, & West, 1999; Nevison, Hurst, & Barnard, 1999). Both rats and mice in unstimulating cages will electively consume pain- or anxiety-relieving drugs, supporting their experience of compromised well being (Bardo, Klebaur, Valone, & Deaton, 2001; Sherwin & Olsson, 2004).

Laboratory environments also impinge negatively on rodents' sensory systems. Husbandry and experimental procedures are performed at light levels that can rapidly cause retinal atrophy and cataracts (Burn, 2008; Rao, 1991). Computing equipment, cage washers, hoses, running taps, squeaky chairs, and some fluorescent lighting can produce intense ultrasonic noise capable of triggering seizures, reducing fertility, and causing diverse metabolic changes (Milligan, Sales, & Khirnykh, 1993; Sales, Wilson, Spencer, & Milligan, 1988). Cleaning agents, perfumes, and companion animal scents on human handlers are also aversive to rodents (Blanchard et al., 1998; Burn, Peters, & Mason, 2006; J. L. Williams, 1999). Gustatory deficits relate not to aversion but to deprivation from the variety of tastes normally available to these omnivores, owing to the processed foods typically fed them in the lab (Burn, 2008).

Traditional laboratory feeding regimens further contribute to the animals' unstimulating living conditions. Rats and mice are known for their catholic tastes. Laboratory rodent pellets or powders, supplied ad libitum, are monotonous (Sherwin, 2002), providing little of the variety of textures and flavors provided by natural fare (Jennings et al., 1998). Foraging also takes up a large proportion of a wild rodent's waking time; it is an activity of inestimable importance to the animal's psychomotor experience. Rats and mice will forage, even when food is freely available to them (Neuringer, 1969); this attests to the desirability of giving these animals foraging opportunities in captivity.

If confined rodents are faring poorly, we may expect that animals in more wildlike enclosures fare better. Morrison (2001) reported that rats in pens had better body condition, appeared cleaner, were more inquisitive and friendly, and appeared less fearful of personnel (came out of shelters during morning checks) than rats housed in cages. Pen housing also appeared to stem aggression (Morrison, 2001). Serious fights were not seen among the feralized albino rats, whom Boice (1977) observed in a large, outdoor pen over a 2-year period; these animals showed better health and lower mortality than did a control group of rats housed in typical wire cages.

Being caged in a laboratory does not occur in a vacuum. The effects of caged confinement are exacerbated by other vicissitudes of laboratory life. Most rodents in labs are there to be used in experiments or testing procedures deemed immoral for human participants because of the harm they may cause. Nonexperimental routines such as blood collections, injections, and oral dosing also elicit pronounced stress

responses—rapid, nontransient elevations in blood corticosterone, glucose, heart rate, and blood pressure (Balcombe et al., 2004).

The current trend toward environmental enrichment is positive, but an enriched cage is still fundamentally impoverished. A cage containing nesting materials and shelters, which are the usual limits of enrichment provided (Hutchinson, Avery, & Van deWoude, 2005), still thwarts normal activities and dispersal patterns. Enriched caged animals cannot exercise control over where they go. They cannot forage or burrow. They cannot explore or escape aversive noises, odors, or (sometimes) lights. Nevertheless, many environmental enrichment studies report, a substantial proportion of animals develop behavioral stereotypies in the “enriched” condition (Callard, Bursten, & Price, 2000; Powell, Newman, McDonald, Bugenhagen, & Lewis, 2000; Würbel, Chapman, & Rutland, 1998; Zimmermann, Stauffacher, Langhans, & Würbel, 2001).

THINKING OUTSIDE THE CAGE

Quality of life for rodents in laboratories appears to be severely compromised by the cumulative effects of loss of freedom, pain, and morbidity associated with experimental or testing procedures and the stresses of husbandry routines. Wild conditions of *Mus musculus* and *Rattus norvegicus* contrast starkly to those in the research laboratory. Standard laboratory floor space for rats and mice differs from the smallest wild home ranges by a factor of several hundred.

To these measurable physical disparities must be added the indeterminate psychological effects of lack of freedom and the inability to exert control over one's living circumstances (Webster, 1994). Studies have shown repeatedly that animals are strongly motivated and probably find it rewarding to exercise control over their environments. Confined wild-caught deer mice repeatedly turned on and off (or otherwise modified) any suitable variable placed under their control: motor-driven activity wheel, lights, or sound and ability to visit a nest or platform, to patrol, traverse mazes, or gnaw wood (Kavanau, 1963).

In contrast to captivity, animals in the wild are seldom forced to endure conditions from which they cannot escape or reduce in severity by appropriate behavior (Kavanau, 1967). Pursuing the natural activities that mice or rats normally pursue is what defines the animal's “telos” or ultimate end (Verhoog, 2005). When we confine these animals in small barren cages, we take away their autonomy and their projects. Psychological well being derives from coping successfully and adapting to life's problems, not from the complete absence of problems that demand coping behavior (McMillan, 2004). A challenging environment with some unpleasant events that the subject can take action to avert or escape (life in the wild) is more conducive to psychological well being than an unstimulating environment that restricts natural behavior and thwarts control over outcomes, many of which in the laboratory are noxious.

How feasible is it to provide naturalistic environments—captive settings that allow animals to engage in basic natural behaviors? It has been done already. For

example, a Swiss team of investigators has studied mice in large open-roofed outdoor pens measuring 400 m², with hay-filled shelters and several wooden boxes (Dell’Omo, Ricceri, Wolfer, Poletaeva, & Lipp, 2000). Naturalistic environments introduce meaningful biological complexity, fulfill animals’ ethological needs, and help to foster normal behavioral and brain development (Würbel, 2001, 2002). It has been demonstrated that variation is strongly resistant to efforts at standardization (Crabbe, Wahlsten, & Dudek, 1999). Therefore, for biologically meaningful results, natural variation resulting from naturalistic housing may be seen as more useful than variation derived from keeping rodents in rows of identical, small, sterile cages (Würbel, 2002).

Substantial research has been done on farmed animals toward identifying key stimuli and resources and developing naturalistic environments that meet behavioral needs (Broom & Fraser, 2007). For example, the Stolba family-farm system affords commercially raised pigs opportunities to build sheltered nests and to root and exercise outdoors (Stolba & Wood-Gush, 1984; Wechsler, 1996). Legislation—such as the EU phaseout of factory-farming practices and recent passage of a California law requiring more space for farmed animals—helps to compel the design and adoption of such systems. There is no comparable legislation yet for animals in laboratories; however, that could change, and comparable reforms should be feasible.

CONCLUSION

Science is emerging from a long period of agnosticism regarding the mentality and subjective experiences of nonhumans (Bekoff, 2007; Panksepp, 1998). Accumulated scientific knowledge of Norway rats and house mice informs us that they have high levels of sentience characteristic of all mammals and are individuals with a quality of life and a significant stake in their own welfare. There is now ample available evidence that laboratory caging represents a serious welfare problem not adequately addressed by the best-intentioned environmental enrichment programs. We may conclude that it is no longer justifiable to confine these mammals to tiny, unstimulating cages for the duration of their lives.

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