Fact or Fiction?

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Of Mice And Men*

With thanks to poet Robert Burns and author John Steinbeck who first used these words.

"Some scientists put sterile dimes under the skin of mice, and what do you think happened? Money causes cancer."[1]

Assume that you are a mouse or rat bred specifically for laboratory testing. To fulfill your role in life, would you prefer to live in a shoebox cage, or a much larger space where you have freedom to move around and interact with others? My choice, the chance to be with others, have some sort of social life and the freedom to move around. I suspect most folks would also opt for this.

Here's why I asked the question. Recently, Hanno Wurbel, a doctoral candidate at a Switzerland University wondered what laboratory mice do after the researchers and technicians go home for the night. He knew that mice living in barren housing often develop bizarre behaviors, such as turning endless backward somersaults.[2]

To satisfy his curiosity he set up a video camera to record the nocturnal activities in his lab. Barry Yeoman reports: "When he reviewed the videotape, Wurbel saw something reminiscent of home movies made at a psychiatric hospital. In the dark, the mice performed the same useless tasks repeatedly, with such a compulsive persistence that Wurbel couldn't help but think something had gone awry in their brains. In one sequence, a mouse climbs the stainless steel walls of its cage, hangs from the ceiling by its forelegs while gnawing on the bars, then drops to the floor, only to repeat the process endlessly. On the other side of the cage, a second mouse performs backflips, one per second, for up to 30 minutes at a time. That left a more chilling possibility. Perhaps the environment was impinging on them in a way that drives them nuts. After all, humans with certain psychiatric disorders engage in stereotypic behavior, too: Autistic children flap their hands or rock back and forth, while schizophrenics repeat the same inappropriate words. Do unadorned cages produce mentally ill mice?"[2] Yeoman further adds, "Much of the research that relies on animals could be using brain-damaged subjects, jeopardizing the validity of the data it produces. This could mean that disease modeling, pharmaceutical research, and tests of chemical toxicity are tainted."

Research Questioned

This isn't the first time questions have been raised about rodents as research subjects. In the late 1950s, Mark Rosenzweig at the University of California, Berkeley, noted that an animal's living environment affects the development of its brain.[2] More recently, here's what Neal Branard and Stephen Kaufman reported: "Many of the apparent anomalies seen in animal experiments, however, merely reflect the unique biology of the species being studied, the unnatural means by which the disease was induced or the stressful environment of the laboratory. The stress of handling, confinement and isolation alters an animal's physiology and introduces yet another experimental variable that makes extrapolating results to humans even more difficult. Stress on animals in laboratories can increase susceptibility to infectious disease and certain tumors as well as influence levels of hormones and antibodies, which in turn can alter the functioning of various organs." [3]

Other Complications

Further complicating the issue is the fact that when rodents are tested for exposure to chemicals and food additives they are often given very high doses. In the assessment that the EPA makes to decide what dose to humans may have a hypothetical one in a million chance of causing cancer, the animal receives an average 380,000 times that human dose.[4]

This is done because researchers have to identify in a relatively short period of time what is generally a low incidence of cancer development.[5]

How high are the doses? Here are examples that read like something you would expect to see in *Mad Magazine*:

- Saccharin given to rats was the equivalent of a person drinking 800 cans of diet soda in a day.[6]
- With safrole, one would have to drink 613 (12 oz) bottles of root beer daily.[7]
- With hair dye, the doses were the equivalent of a woman's drinking (yes, drinking) 25 bottles of hair dye every day for her entire life.[8]
- A 155 pound person would have to eat 82,600 slices of bread every day for a lifetime to be exposed to a dose of furfural comparable to that which causes cancer in rodent tests.[9]
- A child would have to drink 19,000 quarts of apple juice a day for life to equal what was given to mice.[10]
- A person would have to eat 400 tons per day of EDB insecticide laced food to equal the amount fed to rats.[4]
- A person would have to consume 2.5 million of the Perrier mineral water containing benzene (20 ppm) each week to approximate the intake that had sickened rodents.[11]
- Someone of average bodyweight would have to eat 35,000 potato chips (about 62.5 pounds) per day for life to get an equivalent dose of acrylamide as lab animals. (I'm not sure that rodents were used for these tests, but for any lab animal this is a large amount). As Steven Milloy notes, "You might not be able to eat just one Lays potato chip, but 35,000?[12]

All this leads the *Wall Street Journal* to say: "There is no substance, no indignity rodents haven't endured. They can probably sprout tumors at the sight of an approaching lab coat."[13] Others have described this approach as "mathematical sleight of hand,"[14] "trans-science,"[15] and "mouse terrorism."[13,16]

Michael Fumento says this: "The day will come, not too long from now, when dosing animals with massive amounts of chemicals and then declaring that this predicts cancer in humans at low doses will be literally laughed at, in the same way we now laugh at witch doctoring and entrail reading."[17]

High Doses Questioned

Lois Swirsky Gold and her colleagues report: "Evidence is accumulating that cell division caused by the high dose itself, rather than the chemical *per se*, is increasing the carcinogenic effects and, therefore, the positivity rate. High doses can cause chronic wounding of tissues, cell death, and consequent chronic cell division of neighboring cells. This is a risk factor for cancer because each time a cell divides, the probability increases that a mutation will occur, thereby increasing the risk for cancer. At the low levels to which humans are usually exposed, such increased cell division does not occur."[18]

Gold *et al* also report: "Historically, standard practice in regulatory risk assessment for chemicals that induce tumors in high-dose rodent bioassays has been to extrapolate risk to low dose in humans by multiplying rodent potency by human exposure, *i.e*. by multiplying linearity in the dose response. Without data on the mechanism of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be zero. Several mechanisms have now been identified that indicate that carcinogenic effects at the high doses of rodent tests would not be relevant to the low doses of most human exposures. Under the new Guidelines for Cancer Risk Assessment from the EPA, these mechanisms are to be considered in evaluating the dose-response of risk assessment and relevance to humans. The default linear extrapolation has been replaced by this more scientific approach".[19]

An interesting comparison involving humans is one with beta carotene. A Finnish study of beta-carotene in human diets may have been thrown off by just a 15-fold increase in dosage.[20] There's some fuzzy math here. We expect meaningful information from a 380,000 times dose for rodents when as little as a 15 times dose for humans messes thing up.

That's not all. Thomas Moore reports that with prescription drugs, animal cancers are often seen near the comparable human dose since animals can rarely tolerate unrealistically large amounts of these potent materials.[21] So, we get alarmed when a rodent gets cancer from a dose of hundreds of thousands times the human equivalent dose of some chemical, but with a drug we only use the amount a human would typically ingest. Go figure!

There are other items to consider. Steven Austad notes: "Any medical research specialist can give you chapter and verse on how rats and mice differ from humans in her particular specialty, be it heart, kidney, brain, or muscle function. Rodents have vastly different dietary requirements than humans. They are poisoned by some chemicals that are harmless to humans, and vice versa."[22]

Here are some specific differences between rodents and humans:

- Rats and mice do not undergo anything similar to human menopause.[23]
- Rats have no dietary source of ascorbic acid and they have no gallbladder. Their six pairs of mammary glands suggest an increased likelihood for tumor development compared to humans.[24]
- Rodent strains are specially bred to be prone to cancer (Sprague-Dawley rats, Fischer Rats, and B6C3Fl mice).[25]
- Recently, it was reported that A/J (A) mice were sensitive to nickel sulfate aerosol exposure, while C57BL/6J (B6) mice survived nearly twice as long.[26] Want to wager on which strain will be used for further testing of the effects of nickel?
- Rats are unable to vomit, so when a rat ingests a toxicant, it is unable to expel the material from its stomach.[27]
- Mouse cells turn cancerous much more easily than human cells.[28]
- Mice vary greatly from strain to strain in their sensitivity to the hormone estrogen.[29]
- Rats respond differently to short-term starvations. Steven Austad observes: "If you starve a laboratory rat for a day, it can run farther and longer than if it were full fed. Starve humans for the same amount of time, and exercise endurance plummets."[22]

Summary

The contributions of animal research to health, safety, and well-being of both humans and animals have been enormous. Without animal research, very few of the medical advances we expect today for ourselves and our loved ones would be possible. The effectiveness of penicillin and other antibiotics that have saved tens (perhaps hundreds) of millions of lives was established through research on mice and other rodents.[30] Other advances from studies involving rodents include modern anesthesia and neuromuscular blocking agents, therapeutic use of sulfa drugs, and the discovery of DNA.[31]

However, high dose testing of rodents for chemical toxicity is another issue by itself. *The Wall Street Journal* sums it up best: "The net result of this type of research is that thousands of harmless substances are branded as carcinogenic. Everything from dioxins to diesel exhaust has been shown to cause cancer in these poor creatures and are, therefore, branded by the EPA as potential carcinogens. The costs to industry, and hence the ordinary consumer, are vast. The only people who benefit are the junk scientists and their patrons, the bureaucrats."[13] ***P&SF***

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