The Ethical Challenges of Animal Research

Honoring Henry Beecher's Approach to Moral Problems

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Abstract: In 1966, Henry K. Beecher published an article entitled "Ethics and Clinical Research" in the *New England Journal of Medicine*, which cited examples of ethically problematic human research. His influential paper drew attention to common moral problems such as inadequate attention to informed consent, risks, and efforts to provide ethical justification. Beecher's paper provoked significant advancements in human research policies and practices. In this paper, we use an approach modeled after Beecher's 1966 paper to show that moral problems with animal research are similar to the problems Beecher described for human research. We describe cases that illustrate ethical deficiencies in the conduct of animal research, including inattention to the issue of consent or assent, incomplete surveys of the harms caused by specific protocols, inequitable burdens on research subjects in the absence of benefits to them, and insufficient efforts to provide ethical justification. We provide a set of recommendations to begin to address these deficits.

Keywords: Henry K. Beecher; Cambridge Declaration of Consciousness; assent or dissent in animal subjects; animal research; animal experimentation

Many problems with animal experimentation, including an absence of thorough ethical evaluation, are analogous to those that plagued human experimentation in the twentieth century. In his 1966 pathbreaking paper, "Ethics and Clinical Research," Henry K. Beecher located many ethical deficiencies in human subjects research.[1] Beecher concluded that human research was commonly conducted with inadequate attention to informed consent, risks to participants, and ethical justification. Thought to be one of the most influential papers ever written in bioethics, in his work Beecher showed that unethical practices were more common than had been assumed. In this article, we show that there are significant parallels between Beecher's observations about human research in 1966 and contemporary problems with animal research.

From Beecher's Ethical Concerns to an Ethical Code

Frustrated by the lack of response to a 1959 article he published in *JAMA*[2] and his related book,[3] Beecher voiced to a group of journalists at a 1965 conference his concerns that "breaches of ethical conduct in experimentation" were "almost, one fears, universal."[4,5] Soon after the conference, the *New England Journal of Medicine* accepted a version of his presentation after a previous version of the paper had been rejected by *JAMA*.

Beecher's 1966 paper appeared with 22 examples of protocols from the post–World War II era, which he assessed as ethically problematic cases of human research.

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Beecher clearly targeted mainstream science.[6] Although he demurred from providing specific citations associated with the work he criticized, he asserted that the experiments he chose were conducted in and funded by large, mainstream institutions and were published in prestigious journals. His observations of human research led him to extract a set of concepts and norms that he thought essential to the ethical conduct of research with subjects:

1) Quoting Pope Pius XII, he stated that researchers should acknowledge that "science is not the highest value to which all others . . . should be subordinated."[7] In other words, the needs of science should not always trump other considerations.
2) It is essential to strive for an adequate consent from possible subjects. Although Beecher acknowledged difficulties in securing what would later be called informed consent, he emphasized that it was important that subjects or their surrogate decisionmakers understand what was currently known about the hazards of a particular research project, and that they authorize their use as research subjects.
3) Ordinarily, patients will not volunteer to risk their lives for science, a reluctance that researchers must not circumvent. Beecher described how physicians and researchers dangerously assumed a "god-like prerogative of choosing martyrs for science."[8]
4) The gain anticipated from an experiment should be commensurate with the risk involved.
5) Whether or not an experiment is ethical can be assessed on the basis of study design, provisions for adequate consent, known risks, anticipated benefits, and the like. Beecher emphasized that an experiment that is unethical at its inception cannot rightly be judged ethical after its completion on the basis of its results.
6) The increased availability of funds for research coupled with publication requirements for professional advancement have created a perilous environment that can blind researchers to the necessity of careful ethical evaluation of research topics and methods.

Beecher's article eventually influenced the development and implementation of federal rules governing human research conduct in the United States, but the changes made were not always those Beecher envisioned. He was critical of the human research environment, but he argued that solutions should involve an identification of and focus on the relevant moral virtues that investigators should strive to inculcate and realize in their professional activities.[9] Beecher did not believe the best protection for patients was an ethical code with principles and rules, and he did not aim to stifle research or provoke outside intervention. However, the response from the research and regulatory community took the direction of increased internal committee review at institutions and changes in National Institutes of Health requirements concerning informed consent and local review boards.[10] Within a decade, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was authorized by the U.S. Congress, and four years later it produced its Belmont Report, which presented the ethical principles that continue today to serve as guidelines for the conduct of human research.

Reasons for the Urgent Need for a Beecher-Style Examination of Animal Research

In the United States, the Laboratory Animal Welfare Act was passed in the same year that Beecher's article was published, 1966, but only after public outrage grew in response to two popular magazine articles, which graphically displayed the consequences of the illegal acquisition and inhumane treatment of dogs used for research.[11,12] After it passed, the act set licensing requirements and minimum standards for the handling, sale, and transport of some species designated for federally sponsored laboratory research, but the reach of the law stopped at the laboratory door and did not cover research activities.

At that time and since, researchers worldwide have been largely directed by regulations that focus on the "three Rs" framework proposed by Russell and Burch in 1959. This framework emphasizes *replacement* of animals with nonanimal research methods, *reduction* in the numbers of animals used in experiments, and *refinement* of experimental techniques to reduce pain and suffering.[13] Although the three Rs structure provides useful guidance, it does not directly consider questions about the ethical justification of animal experiments when alternatives or reductions in pain and numbers are claimed to be unavailable. That is, the three Rs do not explicitly include an important fourth R, *refusal*, even when the level of suffering is predicted to be extreme and unrelenting.[14]

Meanwhile, scientific research has resulted in rapidly expanding evidence about animal cognition and emotion. On July 7, 2012, a prominent international group of neuroscientists gathered at the University of Cambridge to reassess the neurobiological substrates of conscious experience and related perceptions, emotions, and behaviors in humans and animals. In what could prove to be a pivotal moment, this prestigious group issued a declaration on consciousness that "the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Nonhuman animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates."[15] Since sentience is seen as a necessary condition for suffering, the presence of this capacity should raise the level of ethical concern and of appropriate ethical protection.

What we are learning about animals' mental lives and, relatedly, about the ways in which they can be harmed motivates further ethical examination of the human use of animals, including their use in scientific research. Growing ethical concerns about animal research are evident in public sentiment, as well as in legal and educational endeavors. According to the Gallup Organization cross-sectional survey of approximately 1,000 Americans, opposition to animal testing increased from 33 to 43 percent between 2001 and 2011.[16] There are also growing concerns about the possibility of validly translating animal research findings to the human conditions they are intended to model. There are acknowledged inadequacies in the predictive value and evidential weight of animal experimentation,[17] and systematic reviews and meta-analyses have demonstrated that findings in animals are not necessarily reliable indicators of the promise and safety of human clinical research.[18,19]

Two years before the Cambridge Declaration on Consciousness was released, the Institute of Medicine (IOM) was asked by the National Institutes of Health to render an opinion about whether chimpanzees were necessary for the advancement

of biomedical research. In December 2011, the IOM committee—which was composed of scientific research experts and a single bioethicist—concluded that chimpanzees were largely unnecessary for ongoing medical research. In spite of its narrow task, the committee also concluded that demonstrating scientific necessity does not imply that an experiment is adequately justified, and decisions about the use of chimpanzees in research must take ethical issues into account.[20] Ethical analysis of the animal costs of involvement is therefore not an optional part of the justification process.

Despite these advancements, the number of animals used in experiments each year has continued to climb, similar to the growth Beecher noticed in the expansion of human research in the mid-twentieth century. In the United States, more than half a billion animals are used in research each year.[21,22] In the past decade, the National Institutes of Health budget for extramural grants increased from approximately $15 billion to $30 billion. Almost 50 percent of these grants provide direct support for animal research, and this percentage has been fairly steady nearly every year.[23] These figures do not include intramural funding provided by universities, private institutes, foundations, or corporations or funding for animal research within other government agencies, including the Department of Defense, Environmental Protection Agency, Food and Drug Administration, or United States Department of Agriculture.

Examples of Ethically Problematic Animal Experiments

Following Beecher's lead, we have selected cases from leading international research institutions, funded by large, mainstream public and private institutions, and published in reputable journals by respected investigators. We have not included older, well-known cases such as the University of Pennsylvania head injury studies or the case of Silver Spring monkeys but instead have focused on more recent studies that are largely without a controversial public or legal history. Like Beecher, we are concerned with calling attention to a range of ethical problems that appear to be either neglected or denied during the regular conduct of animal research. We do not target individuals involved in these studies, but we do list in the references all who published the work.

A Method for Measuring Inescapable Pain in Mice

In a 2010 study, researchers placed mice singly in Plexiglas observation cubicles with digital video cameras positioned to film their faces before and after administration of 14 different forms, durations, and severities of pain stimuli.[24] The goal of the study was to develop an observational coding system that identified facial features of mice experiencing different degrees of pain. Researchers hoped that the coding system would be useful in studying the neurobiology of pain and would perhaps provide a useful tool for the identification and treatment of pain in veterinary medicine. They found that orbital tightening, nose bulge, cheek bulge, altered ear, and whisker position reliably signaled different degrees of the presence of pain in mice.

Researchers applied painful stimuli to restrained mice by injecting noxious chemicals into their ankles, hands, and feet, and by hind paw incisions. They induced bladder inflammation with a chemical known to cause painful cystitis in humans

and injected acetic acid into their abdomens, causing them to writhe in pain on the test chamber floor. Researchers placed mice on hot plates, had their tails submerged in hot water, clamped metal binder clips on the tips of their tails, and induced nerve injury that is known to cause severe distress in humans. Some painful stimuli remained active for as long as four hours. The only time an analgesic was provided was to determine its experimental effects on facial expressions. The mice were kept alive for about two weeks thereafter, without pain relief.

This type of study raises ethical problems that are unresolved and largely unattended to by researchers, oversight committees, and journals that publish the research. For example, there is an implicit acknowledgment that mice experience pain commensurate with human pain, yet no attempt is made in the paper to explain why inescapable pain should be ethically permissible in mice when it is not permissible in research with human subjects. There is no discussion of whether the use of inescapable pain violates an acceptable threshold for suffering or of whether such a threshold exists. The paper contains no exploration of the relative moral importance of human or animal suffering or how the risk for suffering is weighed against potential benefits to research subjects or others.

The scientific value of the "grimace scale" hinges on whether the scale provides significant information about pain perception not otherwise available. As described, the scale requires specialized equipment to visualize and record animal faces in many different experimental contexts, and significant training time to develop and maintain standards of reliable and valid scoring. When a researcher places a mouse on a hot plate, in order to study the effectiveness of an analgesic or brain lesion in a presumed pain center, the animal's latent ability to step away from the heat source provides a level of measurement with precise intervals. It is unclear how knowing the qualitative shape of the animals' cheeks, whiskers, or eyes adds anything to the measurement. Seeing a mouse writhing on the floor following an abdominal injection of acetic acid is sufficient evidence of the severity of the suffering experienced by the mouse.

As for the vague reference to adding to the pain assessment armamentarium of clinical veterinarians, the authors do not discuss how facial data can supplement or replace established behavioral measures like lethargy and body guarding, or subtler signs known to animal behaviorists. Nor do the researchers address harms introduced outside of the experimental protocol, from birth to death, including harms that mice experience based on their empathic tendencies or harms associated with lack of sleep, unnatural settings, and confinement. The easy availability of mice for research protocols could be seen as a driving force for the selection of these individuals for these experiments, burdening this group of animals in ways that are reminiscent of the burdens historically placed on easily accessible human subjects. Is the gain anticipated from these experiments truly proportional to the risks involved, and would such proportionality justify the research? No such ethical issues are discussed in the published article, which also suggests deficiencies in the editorial review process.

Experimentally Inducing Terminal Heart Failure in Dogs

In a series of papers published in journals of the American Heart Association,[25,26,27] researchers studied the molecular effects of a frequently used but marginally effective therapeutic intervention—cardiac resynchronization therapy (CRT)—for heart failure.

Researchers first created symptoms of heart failure in dogs by surgically implanting a pacemaker, which artificially accelerated their heart rates. Dogs were sedated, intubated, and anesthetized as a surgical opening to the chest to expose the internal organs (left-lateral thoracotomy) was created and pacing wires were placed in the cardiac tissue. After recovering from surgery, the hearts of the dogs were paced at 240 beats per minute for up to one month. This heart rate is roughly twice what would be expected in most breeds under normal conditions.

As a result, terminal heart failure was induced and was determined clinically by symptoms of lethargy, anorexia, chronic shortness of breath (dyspnea), or accumulation of fluid in the abdominal cavity (ascites). Once a clinical endpoint was reached, the dogs in the experimental group underwent CRT, whereas controls continued in the accelerated pacing mode without treatment. After several additional weeks, all the dogs were terminally anesthetized, and researchers surgically harvested their hearts. It was found that besides "slightly" improving the mechanics of heart function and improving a number of molecular imbalances, cardiac cell death was reduced in the treated group.

In terms of the costs to the animals, none of the papers address the pain, discomfort, or suffering nearly to death that occurred in these experiments. Humans experiencing this clinical state report high levels of fear and panic in response to not being able to breathe normally. Exhaustion, abdominal discomfort, and depression add to the array of expected harms. The papers offered no reason to doubt that the dogs in these studies experienced analogous harms. Further, there was no elaboration of incidental harms incurred from reduced quality of laboratory life in general or factors related to the invasive procedures, including the physical, psychological, and social harms associated with separation from the dogs' social groups, limited social stimulation, episodes of physical restraint during required testing and wound checks, threat of additional distressing manipulations, and reduced comfort due to postsurgical malaise. Even if appropriate care and pain control were provided, the ability of the dogs to live the full canine life for which they were prepared by evolution was stunted.

Is it possible to meaningfully compare the harms with the accrual of important knowledge and to justify the harms in this manner? The researchers do not make this claim. They merely say that getting this type of information from human participants would be "difficult," presumably because it would involve challenges related to the design, review, and recruitment of human subjects, and it would take time to collect postmortem tissue. The researchers avoided perceived difficulties posed by human research and instead conducted a harmful set of experiments that do not benefit the animals involved and may not in the end help treat clinical conditions of heart failure in humans.

Maternal Deprivation of Monkeys and Psychological Harms

An ongoing longitudinal experiment examined the effects of various forms of early social deprivation in rhesus monkeys on physical and mental health.[28] The monkeys were randomly assigned at birth to one of three rearing conditions: mother rearing, peer-only rearing, and surrogate-peer rearing. Maternally reared monkeys remained with their mothers from birth and were raised in larger cages with other monkeys. The deprived monkeys were forcibly removed from their mothers at birth and were first raised alone in an incubator for at least one month. Afterward,

peer-only reared monkeys were placed with three other similarly raised age mates in a single cage. Surrogate-peer-reared monkeys spent 22 hours per day alone in a cage with an inanimate "surrogate" mother (a terrycloth-covered water bottle) and had 2 hours each day to socialize with a group of three other same-age monkeys reared in the same manner. Between 6 and 12 months of age, all monkeys born in the same year were placed in a single mixed social group intended to provide social experience to the deprived groups. This maneuver required that mother-reared animals be separated from their mothers at that time.

Raising monkeys without access to mothers has a long and controversial history. Studies conducted by Harry F. Harlow beginning in the late 1950s were initially designed to investigate the importance of physical contact to the development of mother-infant attachment.[29] Harlow asserted that "contact comfort" was of primary importance and attachment was not derived secondarily from the reinforcing effects of feeding activities. Some have seen these findings as having reversed a trend in childrearing in which cuddling and hugging were seen as damaging to the human character; thus the results were worth the extreme lifelong harms to experimental animals.[30] However, others have argued that no-touch childrearing was well on its way out, if it was ever in, more than a decade before the Harlow experiments, as a result of influential books such as those written by the pediatrician Benjamin Spock.[31] In this view, images of distressed motherless monkey infants raised on cloth or wire mother surrogates in the end served more of a rhetorical function.

There is no question that rearing monkeys without mothers alone, with inanimate surrogates, or with peers creates several types and levels of harm. Mothers serve as buffers to environmental stress for their infants and teach them about what is to be feared and not feared in the environment. They provide a secure base from which infants can explore and to which they can return for protection, calming, warmth, and nutrition. Mothers also learn to identify and respond to their infants' particular interactional preferences, thus expanding the depth of the reciprocity of their relationship. Raising monkeys without access to these vital inputs shatters the evolved developmental architecture. It is no surprise, then, that deprivation rearing produces animals with a wide variety of deficits, bizarre behaviors, and intellectual dysfunction. Instead of these outcomes providing empirical and ethical reasons for discontinuation—or insisting on a high bar for use—of these practices, they became favored methods of producing primate models of various human pathologies, including depression, self-mutilation, autism, and anxiety disorders.

It was in this tradition that investigators examined the effects of differential rearing conditions on the long-term health status of maternally deprived monkeys. Changes in body weight, prevalence and frequency of treated injuries, illnesses, and the frequency of abnormal behaviors led to the conclusion that the lack of a mother in the early years had detrimental effects on general health, which was not improved by exposure to social experience later in life. Peer-reared and surrogate-peer-reared monkeys were more likely to suffer adverse mental health effects, as indicated by high levels of stereotypies. In human institutionalized children, stereotyped behaviors like those seen in the monkeys are markers for the presence of other social, cognitive, and linguistic abnormalities. Peer-reared female monkeys were more likely to display self-mutilation or to be wounded by others. On the whole, the panorama of harms experienced by maternally deprived monkeys was

revealed to be even more expansive than previously thought. The evidence of the increased presence of diagnosed illnesses is particularly important in that it describes the presence of pain and distress levels beyond the well-known harmful effects of deprivation. Although not stated in the research, the stress-illness relationship might also produce many undiagnosed illnesses and consequent harms that reside below the normal threshold of clinical recognition.

The researchers implied that because this research initiative had been ongoing for many years and had provided useful insights about development in the past, the original justification should stand for current experiments. Setting aside questions of the adequacy of the original justification, this approach values past conceptions of what constitutes ethically acceptable research conduct and denies the normative importance of accumulating knowledge about other relevant decisional factors. Researchers claimed that, from an experimental design perspective, these monkey studies, unlike human studies, contain the crucial attribute of animals being assigned to groups completely at random, thereby reducing the possibility of bias. Investigators claimed that because human studies that met such expectations as randomization to treatment and control groups and adequate sample size would be "challenging" to create, the use of animal experiments is justified by their relevance for the diagnosis and treatment of human illnesses. However, in recent years, well-designed studies of human children tragically raised under detrimental conditions have been undertaken with scrupulous attention to experimental design and statistical analysis. The work of Michael Rutter and colleagues,[32] who have followed the plight of early mistreated adoptees from Romania into Western Europe in the 1980s and 1990s, is one case in point.[33]

In addition, the researchers declared that invasive assessments of physiological, genetic, and neurological factors in animals are not precluded by the ethical restrictions that apply in the case of human subjects. They do not explain why these ethical restraints apply to humans but not to a species that can be comparably harmed. Overall, the question of why harmful experimental designs that are impermissible with human subjects are acceptable in animal subjects specifically selected on the basis of their constitutional similarity to humans is not discussed. Moreover, the human studies referenced previously suggest that it is a mistake to presume that valid human data are in fact unavailable.

Inducing Posttraumatic Stress Disorder in Rats

In a 2008 study, researchers exposed adult male rats housed in pairs in Plexiglas cages to two "acute stress sessions" and behavioral and physiological tests.[34] During each session, rats were restrained and immobilized in plastic cones and were placed in triangular wedges in a circular Plexiglas pie enclosure with other rats. The rats were then taken to a room where an unrestrained cat was placed on top of the rat enclosure, which was smeared with canned cat food. Although the cat was unable to physically touch the rats, the rats could smell, hear, and see the cat but could not escape. The rats were kept in this situation for 45 minutes. The first session was conducted in the light, and the second session was conducted in the dark; the sessions were separated by 10 days. The second session was intentionally designed to expose the rats to a "traumatic re-experiencing of the original event, in a manner analogous to the intrusive reliving of traumatic memories by people with PTSD,"[35] and to reinforce neuroanatomical changes in the amygdala,

a subcortical structure involved in emotional response and regulation. Between the sessions, the rats were kept in unstable housing situations in which the rat pair combinations were regularly changed for about one month. This type of unstable housing was used because it is known to detrimentally affect rats. After the experiment, blood was collected through a tail incision to determine stress hormone levels, and the rats were placed in a Plexiglas tube within a warming chamber for five minutes to increase blood flow to the tail to measure heart rate and blood pressure via tail cuffs, likely increasing pain at the incision site.

After one month, the rats were then put through behavioral and physiological testing designed to measure anxiety, startle response, learning ability, cardiovascular activity, and stress hormone activity. Placing the rats inside a small Plexiglas box with a sensory transducer inside a larger startle monitor cabinet tested startle response. Acoustic stimuli included multiple bursts of white noise in sequentially increasing decibels; note that this species is very sensitive to sounds that are not detected by the human ear. Learning and memory tests were based on performance in a water maze. Similar tests have been used to induce depression and learned helplessness in mice. Various combinations of these experiments were employed to determine the effects of "acute stressors" and social instability on the rats' development of signs of posttraumatic stress. After all of the behavioral and physiological testing, the rats were returned to their cages for an hour. After that delay, the animals were decapitated while conscious and without pain control, despite indications that the rat brain is capable of processing pain stimuli for approximately five to six seconds following the severing of the spinal cord.

These experiments illustrate a fundamental problem in psychiatric experiments involving animals. The problem consists of a justificatory dilemma, stemming from the need for both ethical and scientific justification and the difficulty of claiming to have both with respect to a particular line of research or protocol. The more researchers emphasize *similarities* between animals and humans, the more they threaten the prospects for ethically justifying the experiment in question; the more researchers emphasize *differences* between animals and humans, the more they threaten the prospects for scientifically justifying the experiment.

The use of rats in the experiments discussed in this subsection relies on the fact that humans and animals share a capacity for positive and negative emotional states, cognitive achievement and impairment, and analogous psychopathology.[36,37] Remaining physically, cognitively, and emotionally intact—through the expression of natural, unobstructed behaviors—is critical to the well-being of these animals.[38,39] However, the mental and physical well-being of animals is intentionally manipulated in psychiatric experiments such as these to produce various forms of psychopathology, including posttraumatic stress, depression, anxiety, and psychosis. The experiment compromises the well-being of rats in ways that are similar to psychological impairment in humans. In addition to the purposeful induction of negative experiences, animals are isolated from pleasure-seeking activities. The study's investigators did not explain why it was justified to inflict emotional and physical suffering on the rats, when it would be ethically problematic to conduct comparable experiments in humans. Finally, it is unclear how these experiments map onto human psychiatric disorders that are largely diagnosed and treated based on a patient's subjective report.

Manipulating Monkeys with Phencyclidine (PCP)

It is well known that drugs of abuse can alter social behavior exhibited by humans while they are intoxicated. With this background, researchers in a 2007 experiment sought to study the effects of social stimulation on drug-seeking behavior in monkeys.[40] The work targeted phencyclidine (PCP), a drug previously used as a dissociative anesthetic but now only illegally produced for its mind-altering properties. To evaluate this social influence question, researchers placed 10 rhesus monkeys in one of two testing conditions. In the first, monkeys worked (i.e., touched a contact relay with their lips) for sips of water or, optionally, water laced with PCP while another monkey was present in an adjoining cage separated only by an open wire mesh panel. In the second condition, all was the same except that the monkey in the adjoining cage was present but not visible. The researchers found that, with another monkey visually accessible, the working monkey emitted more responses and earned many more sips of water and PCP than when the adjoining monkey was not visible. This was seen as demonstrating that the reinforcing value of oral PCP and water was increased by the presence of another monkey. Researchers also found that if they made getting sips of water and PCP more labor intensive, the working monkey stuck with the task longer when another monkey was visible.

Prior to this study, all of the monkeys had been trained to self-administer PCP and water, presumably under significant levels of water and food deprivation. The monkeys were kept in individual cages and were maintained below their normal body weights (at 85 percent of normal body weight) by limiting their daily food allotment. No other data were provided about the monkeys. For example, no information was provided regarding the social and environmental rearing conditions of the animals, which could significantly affect the outcome of the studies as well as their applicability to humans. Without this information we do not know what the monkeys are seeking by increasing their consumption of PCP. It is unclear if the monkeys are seeking the drug's calming effects or its disinhibitory effects that lead to feelings of strength and power, or if there is something else entirely that explains the behaviors of the monkeys. Unfortunately, the researchers did not collect data on the monkeys' behavioral patterns during PCP consumption that might have provided information relative to that question.

What harms did the monkeys undergo for a study with questionable relevance or benefits? First, the apparently full-grown monkeys lived alone in small single cages, inhibiting the expression of many social and nonsocial species-typical behaviors. Their weights were reduced, resulting in individuals usually experiencing some level of hunger. In humans, PCP use can result in trancelike, confused states; disorientation; loss of coordination; distorted sensory perceptions; impaired concentration; disordered thinking; flashbacks; agitation; violence; delusions; and paranoia. It is reasonable to conclude that monkeys under the influence of PCP experience similar symptoms in view of their cognitive similarities to us. Physiological sequelae can include increased blood pressure and heart rate, shallow breathing, nausea and vomiting, blurred vision, excessive salivation, numbness, sweating, and stupor. Long-term, chronic PCP use can create permanent memory loss, seizures, central nervous system damage, and death. Chronic use presents the additional risk of experiencing withdrawal symptoms, including physical distress, lethargy, and depression.

As for benefits that may partially compensate for the aforementioned harms, researchers reported that following lengthy daily experimental sessions, animals had access to toys and fruit and that movies were played for "enrichment." Whether movies improve the life of the animals watching them is a difficult question to answer. What is known is that gazing at videos has been measured in isolated rhesus monkeys at levels as low as 3.2 percent of their available time.[41]

Finally, it is reasonable to conclude that more reliable information about the effect of social situations on human PCP consumption could be obtainable in carefully conducted human studies, interviews, and focus groups with users. If this is correct, then the present study has no scientific or moral justification.

Inducing Severe Lung Injury and Severe Burns in Conscious Sheep

A 2002 experiment induced severe lung injury and a third-degree cutaneous burn in conscious sheep.[42] Fourteen female sheep were randomly assigned to a paracorporeal artificial lung or volume-controlled mechanical ventilation in an unblinded fashion; study personnel were aware of which sheep were placed on an artificial lung and which sheep were placed on volume-controlled mechanical ventilation. The sheep were anesthetized, and a tracheostomy, thoracotomy, and venous cutdown were performed. Researchers burned the sheep over 40 percent of their total body surface areas on both flanks using a propane torch and burned their lungs by delivering smoke from a burning cotton towel through a modified bee smoker. Eight of the sheep were kept on mechanical ventilation, and the other eight sheep were connected to the artificial lung. The sheep were then returned to their cages and awakened. The sheep received mechanical ventilation with the intent of producing acute respiratory distress syndrome (ARDS), one of the most distressing and fatal forms of lung injury. Acute respiratory distress syndrome involves flooding of the small sacs (alveoli) of the lungs, low levels of oxygen in the blood (hypoxemia), and partial collapse of the lungs, resulting in severe breathlessness, chest discomfort, and air hunger. It is typically accompanied by severe panic or anxiety in human patients, if they are conscious. It is considered a life-threatening condition and typically requires immediate intervention, including intubation and respiratory support.

Any animal judged to be in distress based only on physiological parameters was killed. Six of eight of the sheep on the artificial lung and one of six of the sheep on mechanical ventilation survived the five-day experimental period. In the artificial lung group, one sheep died due to sudden pulmonary hypertensive crisis, and another died from sepsis related to pneumonia. At autopsy, this sheep had purulent airway secretions, which is comparable to a death due to drowning. Four sheep in the mechanical ventilation group met distress criteria based on hypoxia (suffocation), and another was killed after becoming bradycardic and hypotensive (signs of cardiac shock). All other sheep were killed after the end of the five-day period.

Researchers stated that all animals received treatment that met criteria for "humane care" according to the 1996 Guide for the Care and Use of Laboratory Animals and that the Institutional Animal Care and Use Committee (IACUC) approved the study. Researchers reported that their management paralleled "our standards of patient care," including daily rounds, involvement of a veterinary anesthesiologist, and medical students who volunteered for 24-hour cage-side

care seven days per week (though it is doubtful that medical students are competent to provide veterinary care for sheep). IACUC personnel, also without veterinary expertise, made daily rounds to check compliance with the animal management protocol.

Despite intense involvement of the animal use committee and strict adherence to the guide, the sheep—beyond any reasonable doubt—experienced tremendous suffering. Burns involving 40 percent of body area result in multi-organ failure and are typically fatal, and morbidity and mortality rates double with smoke inhalation injury. Because the extent of the pain and suffering engendered by these procedures was predictably high at the inception of the study, it could be argued that this experiment exceeded any ethically acceptable level of harm, regardless of any human health benefits that might result from the study.

Manipulating Chimpanzees to Study the Neural Basis of Chimpanzee Gestures and Human Words

A 2008 study cited by the IOM Committee on the Use of Chimpanzees in Biomedical and Behavioral Research demonstrated the use of the committee's standard for chimpanzees to "acquiesce" to (i.e., not visibly resist) research participation.[43] The study was designed to determine whether the chimpanzee inferior frontal gyrus (IFG), assumed to be evolutionarily related to the linguistic centers of the human brain, functioned during nonverbal communication.[44] In the experiment, chimpanzees were lured from their social groups with food, held in isolation, and offered a sweet solution containing a radioactive neural tracer. Next, the chimpanzees participated in either a control condition involving handing stones to a human tester for a food reward or a communication exercise in which they spontaneously tried to get the human tester to provide their preferred foods. Subsequently, the chimpanzees were encouraged by voice and physical signals to present their arms, which they had been trained to do through contingent rewards, and were injected with an anesthetic. They were next placed in a series of two brain scanners, which mapped activity during the tests. The chimpanzees did not have the opportunity to resist this phase, because they were immobilized by the anesthetic. Data showed that the IFG did become selectively activated during the communication exercise, supporting the researchers' hypothesis. After recovery, the chimpanzees remained separated until the radioactive tracer was completely eliminated.

The IOM committee concluded that because the study did not use methods invoking threat or fear, it met their criteria for acquiescence and other criteria for using chimpanzees in an experiment. However, the chimpanzees' behaviors do not satisfy criteria for a form of informed consent or even "assent" as used in human pediatric studies. Informed consent and assent require a combination of voluntariness (with the opportunity to withdraw consent/assent), an adequate understanding of relevant risks and benefits (although less understanding is generally required for assent than for informed consent), and explicit authorization or approval, whereas acquiescence merely implies some form of initial submission. This experiment failed to meet conditions involving understanding, voluntariness, and authorization. For example, it is unclear whether the chimpanzees, once in the experimental space, could cease participation at any point and return to their social groups or which behavioral gestures and signs would constitute such a signal. Researchers had no way to determine if the chimpanzees

feared the possibility of negative consequences (including punishment) if they did not comply with the experimental protocol. Whether the chimpanzees were able to anticipate what would happen to them after they were coaxed into separation and later received the sweet tracer and anesthetic injection would depend on the extent of their experimental history with such procedures and their memory of those experiences. An experimentally naïve subject in this circumstance could merely execute a conditioned response previously established by rewards. Once the chimpanzees had been injected with the tracer, they were prevented from returning to their groups until the researchers were satisfied that the radioactive material had been eliminated.

The meaning of acquiescence seems to boil down to the exclusion of fear-based and pain-based incentives at the juncture of participation choice points. Although this is certainly a welfare improvement, it does not respect the capabilities of autonomy in the chimpanzees.[45] Even if we cannot obtain full informed consent from chimpanzees or other animals, we should still strive for it in individuals who demonstrate varying levels of autonomy. Whether or how animals demonstrate the potential for autonomous decisionmaking and whether humans are able to recognize it are open questions in the case of many animals. Further, the inability to provide informed consent should not be seen as a condition that justifies use of animals in ways they would resist if they could provide meaningful consent, assent, or dissent. In the case of animals for whom our knowledge of their capacities for autonomy is unclear, it may be ethically imperative to interact with them in ways in which it is plausible to think they would consent to or refuse participation, if they could, based on our understanding of their perceptions, emotions, and behaviors.[46]

Conclusion

The cases we have described are representative of much of the animal biomedical and behavioral research enterprise. Each of the experiments was approved by a federally mandated animal care and use committee. These cases are in certain respects more problematic morally than Beecher's selections. In some cases the level of suffering inflicted on the animals in these experiments was particularly severe. The cases include more than one ethical problem, though we have tried to highlight the central problems in each case. We have identified many problems that are analogous to those Beecher found in human research—for example, inattention to the issue of consent (or assent or dissent), incomplete surveys of the harms caused, inequitable burdens on research subjects in the absence of benefits to them, and unacceptably minimal efforts to provide ethical justification.

Though we selected fewer cases than Beecher did for his paper, we believe the problems of animal experimentation are far more ubiquitous than they were for human experimentation at the time Beecher wrote his article. The design and execution of the studies we have examined, and indeed of any research project involving animals, should include serious consideration of the diverse array of ethical obligations that investigators and sponsoring institutions have to their subjects. The resulting publication should demonstrate that consideration of matters such as the following occurred in a serious deliberation:

1) An estimate of the pain, distress, and other harms likely to be experienced by animal subjects. This estimate should include not only factors at central experimental points of manipulation but also the broader context from birth to death.

The estimate should be accompanied by a statement addressing whether animal subjects appeared to participate in the trials cooperatively or willingly—in a manner consistent with the ideas of assent or acquiescence—or unwillingly, which could be indicated by the absence of cooperation or by resistance.

2) A sustained ethical justification for the experiment, not simply a notation that the project was approved by a responsible review panel or that it follows relevant law.
3) Evidence that the experiment is scientifically necessary, rather than just a potentially useful addition to the literature.
4) A statement explaining why the study or an analogous study cannot be conducted in human subjects who can provide (1) informed consent or (2) assent in cases in which a surrogate decisionmaker can provide adequately informed permission.
5) An explanation of why a relevant study that could not be conducted in humans would be ethically justifiable in animals.

Just as the Belmont Report responded to concerns about moral shortcomings in human research, a similar document is needed to address the problems inherent in animal research. Societies bear responsibility for creating the best possible ethical context for decisions regarding the use of animals in research. Accordingly, it is the duty of the public and professionals within research, regulation, oversight, and publication settings to upgrade standards where they are morally deficient in particular research centers and in broader public policies. The status quo of animal research, as represented in part by the case studies discussed here, cannot withstand close ethical scrutiny. It is paramount for those professionally involved in animal research as well as for the broader society to recognize the unacceptable status quo and to work toward ethically justified reforms regarding the use of animals in research.

Notes

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