**ILAR J**

Volume 60, Number 3, 2019

***Ethical Questions Around Animal Research***

**DeGrazia and Beauchamp. Beyond the 3 Rs to a More Comprehensive Framework of Principles for Animal Research Ethics, pp. 308-317**

Domain 3: Research

SUMMARY: The authors have in press a book regarding animal research morals and ethics (Principles of Animal Research Ethics, Oxford Univ Press), and this article aims to summarize the content and present their proposed moral framework for animal research ethics.

Justifying Timing And Need: This new framework is now timely, as there are these 6 recent developments: (1) growing public concerns about animal welfare; (2) advances in the scientific study of animals; (3) the development of animal ethics as a scholarly discipline; (4) significant gaps in the content of the 3 Rs conception of animal research ethics; (5) growing concerns among scientists about the reliability of nonhuman animals as models for humans; and (6) a persistent but unconstructive perception that fundamentally different moral perspectives on the ethics of animal research are irreconcilable. Authors claim this framework is more suitable than the 3Rs of Russell and Burch, as it meets 3 demands that were lacking: (1) to be ethically defensible, (2) to be politically reasonable, (3) to be practically instructive.

Comparing To The 3Rs: Authors claim their framework adds to omissions of the 3Rs concept by: (1) expanding the focus of the animal welfare to all morally relevant aspects of laboratory animals’ life, such as transport, housing, feeding and companionship, (2) underlining ethical considerations pertaining to human social benefit, including the likelihood of achieving benefit through animal studies and whether and how the prospect of benefit justifies anticipated costs and harms of research and (3) including the support of ethical analysis.

Presenting The New Framework: This framework of core values and basic principles, is  based onto 3 pivotal moral norms – to which reasonable representatives of both the animal research and animal protection communities should be able to agree on: (1) sentient animals have moral status and are therefore not merely tools of research; (2) the only justification for (non-therapeutically) harming animal research subjects is the prospect of substantial and otherwise unattainable social benefits; and (3) permissible harming of animals in research is limited by identifiable considerations of animal welfare.

The proposed framework for animal research ethics comprises 2 core values: social benefit and animal welfare. For each core value there are 3 principles. The principles of social benefit are: (1) no alternative method, (2) expected net benefit, (3) sufficient value to justify harm. The principles of animal welfare are: (1) no unnecessary harm, (2) basic needs, (3) upper limits to harm. Each principle in the framework is a necessary condition of morally justified animal research, meaning that failure to satisfy any 1 of the 6 principles entails a failure of moral justification.

Principles of animal research ethics are examined first. The Principle of No Alternative Method underlines the obligation of a thorough search for possible alternative methods and elimination of chances that a scientifically viable alternative exists, which is the proof that the benefit is not reasonably attainable except through research involving animals, similar to the Replacement of the 3Rs. If the first Principle is satisfied, then the Principles of Expected Net Benefit and Sufficient Value to Justify Harm are sequentially addressed in the cost-benefit analysis. The Principle of Expected Net Benefit includes considerations on the magnitude of the benefit to society and the likelihood to yield it, taking into account rates of successful translation from animal studies. The Principle of Sufficient Value to Justify Harm requires for this benefit to be sufficiently valuable to justify expected harms to animal subjects. This is to be debated in review committee meetings.

Consequently, principles of animal welfare are examined. According to the Principle of No Unnecessary Harm, overlapping with the third of the 3Rs, Refinement, each particular harm must be necessary for and morally justified by scientific purposes. All harms must be minimized, including not only experimental procedures but also all aspects of feeding, housing, transport etc. and harms that might be caused due to negligence. According to the complementing Principle of Basic Needs, animal subjects’ basic needs must be met, including food, water, housing and companionship, as failure to cover those constitutes harm. Exceptions must be justified scientifically, as described above. The final Principle of Upper Limits to Harm forbids inflicting severe suffering for a lengthy period of time, thus setting an upper limit on the harm permitted to be imposed. This shall again include all aspects of animal life and not be limited to experimental procedures and any exceptions shall be carefully justified. This Principle expands on the upper limit to harms of experimental procedures included in the EU Directive. Such limits are missing from the US legislation.

The role of ethics review committees is pivotal. Other issues such as conflict of interest are to be considered.

QUESTIONS

1. According to the moral Framework of Principles for Animal Research Ethics presented by D. DeGrazia and T.L. Beauchamp in ILAR, 2019, which are the two core values in animal research:

a. Social benefit and animal welfare

b. Replacement and reduction

c. Refinement and reduction

d. Personal benefit and animal use

2. List the 2 core values and 6 principles of the moral Framework of Principles for Animal Research Ethics presented by D. DeGrazia and T.L. Beauchamp in ILAR, 2019.

3. Upper limits to harms on laboratory animals are included in:

a. Only the EU Directive

b. Only the US legislation

c. Only the DeGrazia & Beauchamp Framework of Principles for Animal Research Ethics

d. In a and c

e. In a, b and c

4. The moral Framework of Principles for Animal Research Ethics presented by D. DeGrazia and T.L. Beauchamp in ILAR, 2019:

a. Dismisses the theory of the 3Rs as outdated and irrelevant to current research

b. Opposes the theory of the 3Rs presenting contradictory elements

c. Adds to the theory of the 3Rs, including them in a more robust framework

d. Presents a different theory and does not mention the 3Rs at all

ANSWERS

1. a

2. The 2 core values are: social benefit and animal welfare. For each core value there are 3 principles. The principles of social benefit are: (1) no alternative method, (2) expected net benefit, (3) sufficient value to justify harm. The principles of animal welfare are: (1) no unnecessary harm, (2) basic needs, (3) upper limits to harm.

3. d

4. c

**Hvitved. Engaging Ethicists in Animal Research Policymaking, pp. 318-323**

Domain 6: Education, K3 Society issues involving use of animals, philosophy, and ethics of animal use

SUMMARY: Human subject research policymaking has had an ongoing engagement with the ethics community while the role of the ethics community in the animal research policymaking process has been less defined. While some proposals aimed at IACUCs may be effective in instituting certain ethical considerations, this article focused on the federal policy environment level. In human studies, “The Common Rule,” as defined in the Belmont Report, a document developed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,” set which types of activities are and are not allowed and what IRBs should consider when approving research. The Belmont Report laid out 3 ethical principles to guide the development of regulations: beneficence, respect for persons, and justice. The closest thing in animal research are the 3Rs as defined in The Principles of Humane Experimental Technique. The biggest difference is that the 3Rs guide experimental design in the context of current regulations but provide no insight or input on the development of new policymaking. One missed opportunity cited was the lack of ethicists present at the 2016 NIH workshop for the review of NHP research ethical policies and processes. The focus was on scientific progress and human benefit, which is not the only ethically relevant aspect of NHP research. A policymaking environment that is more inclusive of a broader range of stakeholder input should reasonably be expected and produce outcomes that appease a broader range of stakeholders.

QUESTIONS (True or False)

1. The 3Rs provide guidance for policymaking regarding animal use in research.

2. Oversight of animal research in the US is governed by the Animal Welfare Act and the Health Research Extension Act.

3. The Belmont Report is applied to human subject research and animal subject research alike.

ANSWERS

1. False

2. True

3. False

**Nobis. Why IACUCs Need Ethicists, pp. 324-333**

Domain 5: Regulatory Responsibilities; T5/6, K2;

Doman 6: Education; K3, T3

SUMMARY

* There exists an ethical obligation to prevent morally wrong actions and improve those actions when possible. In the field of biomedical research, this obligation is often overseen by the IACUC. Where there is a legal requirement for scientific and veterinary expertise on this committee, none such exists for ethical experts. Philosophical ethicists are equipped with unique skills to recognize morally problematic research design and thus better advocate for the above ethical obligation, while simultaneously ensuring decisions are made in an evidence-based manner. They may ensure the scientific community appropriately acknowledges the ethical dilemma of animal use in research and insofar prompt more thorough scientific justification for such.
* The role of the non-scientist community member may be performed by such an ethicist.
* Philosophical ethicists have received specific training in critical thinking, ethical theory, and philosophy of science. Critical thinking skills enable them to define and clarify terms such as "essential, benefit, and harm," and as such recognize and ameliorate perceived disagreements and establish a more logically sound foundation on which discussion can continue. These skills also empower recognition of invalid or incomplete arguments.
* Training in ethical theories better equips them to explain why an action (e.g. in a proposed protocol) may be wrong. This training ensures that theories frequently adopted by the biomedical research community such as utilitarianism or non-human animals' lack of rights are done so appropriately and with acknowledgement of ethical objections. In doing so, the ethicist may help IACUCs navigate complex and often poorly understood topics.
* Training in the philosophy of science provides the ethicist with an opportunity to train IACUCs in more methodical review of protocols. Furthermore, they may act as more "objective" reviewers in receipt of critique, as there is a tendency for any such critique of research to be interpreted as global condemnation by biomedical research personnel. This is further supported by their status as "community members" without vested stakes in the particular institution.
* Objections to inclusion of ethicists on an IACUC are acknowledged. They will not "stifle research," but rather prevent problematic research and thus promote appropriate critical thinking and arguments. They may not be needed for other aspects of research as those subjects need not face major harm. Perceived disagreements among ethicists are either inappropriately understood or outright misrepresented. Finally, where ethical disagreements do exist, or changes over time are noted, ethicists are best equipped to make observations and proposals for addressing them.

QUESTIONS

1. Which of the following is a committee member specifically required by the PHS policy (OLAW) and not by the AWA (USDA)?
   1. A veterinarian with training or experience in laboratory animal science
   2. A member whose primary concerns are in a non-scientific area
   3. A member who is not affiliated with the institution
   4. All of the above are required by both the PHS and AWA
2. T/F: One individual may not serve as both the non-affiliated member (community member) and member whose primary concerns are in a nonscientific area (non-scientist).

ANSWERS

1. a
2. False

Resources include the [PHS Policy](https://olaw.nih.gov/resources/tutorial/iacuc.htm#5a) and [AWA, section 9 CFR 2.31](https://www.nal.usda.gov/legacy/awic/animal-welfare-act)

**Brill et al. The Symbiotic Relationship Between Scientific Quality and Animal Research Ethics, pp. 334-340**

Domain 3: Research; T2. Advise and consult with investigators on matters related to their research; T3. Design and conduct research

ONE-LINE SUMMARY: This review seeks to explore the complex relationship between scientific quality and animal research ethics while advocating for the development of a detailed “Harm-Yield Analysis” for evaluation of biomedical animal research.

SUMMARY: The authors first discuss what scientific quality is by trying to define it.  They state that ethical justification for the use of animals in research is an extension of utilitarian principles, in that, potentially harmful animal research can be justified only if the need for and potential yield from the scientific study outweigh the harms.  The authors argue that scientific need and the quality of the science itself is just as important and needs to be considered. They cite Russell and Burch’s work and Bateson’s Cube, where the need for sound scientific design was emphasized while seeking to reduce harm.

The “Harm-Benefit Analysis” (HBA) paradigm was introduced, discussing its inclusion in European Union Directive 2010/63, United Kingdom’s Animals (Scientific Procedures) Act of 1986 and the Good Laboratory Practice regulations in the United States. They conclude that HBAs fail to provide a clear path for the ethical consideration of studies that do not provide a clear direct benefit. Additionally, there is a lack of consensus on how to conduct an HBA, where best to consider the quality of the science and how much weight should be given to such a consideration.

Regardless of the potential impact of the stated goals, if the rigor and scientific quality of a study is lacking, the study is more likely to produce untrustworthy or unanalyzable data.  The routine consideration of scientific quality alongside benefit can at least in part compensate for the times when the inherent benefit of a study is uncertain.  The article presents the story of Dr. Ralph Baric and many other examples to highlight that potential benefits can result from high-quality basic science research and should be considered when evaluating the ethics of research with animals.  They remind the reader that anticipation of benefit from a study is by no means a guarantee that a benefit will occur and by using the 3Rs as a guideline and then completing a subsequent ethics analysis comparing both anticipated benefit and scientific quality to the potential harms, a balance between reduction of harm and optimization of the value of the research can be obtained.

Using historical perspectives and considerations of animal research ethics, particularly Bateson’s Cube, a “Harm-Yield Analysis” (HYA) process was introduced, as a balance between potential harms to the research animals on one side vs the combination of anticipated benefits and scientific quality on the other. The article contains a pictorial illustration for better understanding of the process.  They explained that this analysis should include three (3) elements:

1.   Minimum and maximum thresholds for categorical variables and sub-variables be established.

2.   Formulations constructed to suit individual fields more specifically while being careful not to adopt or at least question potential harms that may be thought to be “common practice” in those fields.

3.   Iterative analyses in which the research scientist uses results from initial experiments, updates in the field and animal husbandry best practices, to inform the analysis for future experiments.

The conundrum expressed was how to effectively promote the adoption of the HYA or any framework for the consideration of ethics in animal research.  There is a need to educate the scientific community on the integral link between the ethics around proposed animal research and the quality of the science. To address this issue, the authors advised inclusion in the graduate school curriculum by didactic lectures, examination of real-life case studies focused on animal research in a wide variety of disciplines and opportunities to work through hypothetical scenarios.They also remind that current research scientists must also consider the ethical implications of their work and create environments in which discussion around best practices in animal research are encouraged. They end the article stressing that adoptions of a HYA process will benefit both animal welfare and scientific progress.

QUESTIONS

1.   From the article, list two (2) frameworks for considering ethics of animal research.

2.   According to the article describe Dr. Ralph Baric’s work in the early 1980s.  How did that work impact our lives today?

3.   True/ False: Singly housed pigtailed macaques develop lower CD4:CD8 T cell ratios, have a greater decline in CD4 T cells, demonstrate more CD4 and CD8 T cell activation, and suffer from higher viral loads during acute simian immunodeficiency virus infection compared with socially housed macaques.

ANSWERS

1.  Russell and Burch’s Principles of Humane Experimental Technique (1959) and Bateson’s Cube (1986).

2.   Dr. Ralph Baric defined the structure of coronaviruses and how the virus interacts with host cells and developed mouse models for the study of coronavirus pathogenesis. His work served as an essential foundation for research done in response to the COVID-19 pandemic, guiding the development of mouse models for pathogenesis research and allowing for the swift identification of targets for vaccines and subsequent vaccine development.

3.  True

**Niemi. Harm-Benefit Analyses Can Be Harmful, pp. 341-346**

SUMMARY

Overview:Harm-Benefit analyses (HBAs)  are becoming popular with some regulatory agencies and local institutional animal care and use due to the adoption of HBAs as an international accreditation standard that is employed as an attempt to balance potential/actual pain imposed on animals vs. scientists justification on why it is needed. While in theory, HBAs is a means to avoid or minimize sufferings, it can be flawed due to some factors such as establishing an accurate prediction of benefit due to uncertain nature of experimental outcomes and the eventual value of those results to which there is a risk of disapproving legitimate research proposals and that anticipated harm to the animals must be scrutinized with aim to refine that harm regardless of purported benefits.

Advocacy:The origin of HBA was conceived by Jeremy Bentham (1748-1832). The advocacy is for the moral protection of animals but with toleration of some types of animal research when that experiment has a determinate objective and beneficial to mankind.

A 3-dimensional matrix has been widely quoted to which: 1st axis was a gradient for animal suffering from low to high, 2nd is the quality of research, and 3rd is the certainty of medical benefit. Based on this matrix only proposals that score lower suffering, higher quality and higher certainty should be then allowed to proceed. HBA thereafter has been integral to the official animal experimentation project license evaluation process, and HBAs has been used by other govt. oversight bodies such as the Canadian council of animal care and European union with directive 2010/63/EU both more or less purported that “Harm to animals in terms of suffering, pain and distress is justified by the expected outcome and can reasonably be expected to benefit humans or animals’.

There are also some noted inconsistencies to the application of HBAs, one such, that AAALAC Intl posted in that “IACUC (or comparable oversight bodies), as part of protocol review process, will weigh potential adverse effects of the study against the potential benefits of the research, in contrast , no such analysis pertaining to HBAs is included in US Animal Welfare Act or US Health Research Extension Regulation Act. In addition, neither USDA nor OLAW require IACUC to perform HBAs when reviewing protocols. Thus the absence of regulatory requirements for HBAs under US laws makes AAALAC’s insistence on performing HBAs and confirming their use during accreditation site visits appear inconsistent with AAALAC’s rule of accreditation 2e which informs that “accreditable units shall observe any and all statutes and governmental regulations”.

When Are HBAs Useful:When both harm and benefit can be reasonably predicted, HBA maybe useful to determine the acceptability of animal research proposals. HBAs are also appropriate for preclinical safety and efficacy testing when the degree of the diseases or injury is well characterized for a given patient population that may justify the likely suffering imposed on animals. Whereas, HBAs can and should be performed as advocacy for replacement in vitro assays when maximal harm is known and when the “benefit” of in vivo assay itself vs non animal alternative is no longer  superior to continue.

Example of HBA-Driven advocacy for non-animal replacements:

1.  Potency testing of rabies vaccine (animal use vs replacement in vitro assays)

2.   Mouse teratoma assay to which gold standard is still the use of mice but van cause animal suffering, however, as gold standard manuscripts that omits this assays are subject to rejection. As of current, multiple non-animal alternatives are being done such as gene expression profiles or immunoassays for surface cell antigens.

Inappropriate Applications of HBA:On HBA review: “If actual harm is assigned only to animals subjects, what about the equivalent harm experiences by other sentient being suffering from the same disease or injury under study if the proposed research is not performed?”. As the intent of HBAs, why should “harm” be restricted to intentional pain and distress of animal research and exclude unintentional yet identical pain and distress afflicting human or animals. Although the alternative interpretation is not likely to receive much support, a second limitation of HBAs is the difficulty in assessing benefit when the research proposal involves so-called “basic research” in which no medical application is obvious, intended or may never occur or when even such benefit eventually surface, they can never be estimated or envisioned with certainty, such as cancer immunotherapy to which little is known and years away from breakthrough and was pushed off in a the corner as “little was known about immune systems: and that chemotherapy and radiation treatments are in prominence before. So if HBAs were performed for these protocols under prevailing scientific opinion at an earlier time, would this has been approved? Or denied?  Because experts consensus that “no” certainty of medical benefit or likely benefit would ensue then. Similar to approaches in Alzheimer’s diseases study. What if investigating alternative theories of AD onset and progressions such as viral infection are denied animal experimentation due to “unconvincing benefit” or what if new insights based on previous hypothesis is seen without “obvious” benefits yet vs “harm” will then this thwart approval of future experiments by HBA?

Alternatives to HBAs: Ethical justification besides benefit in formal documents by US institutions. The US Governments principles for the utilization and care of vertebrates animals used in testing, research and training stipulates that “procedures involving animals should be designed and performed with due consideration of their relevance to human, or animal health, the advancement of knowledge , or the good of the society”. “Advancement of knowledge” alone is listed just as worthy a rationale.

Redefining Harm: In addition to the attention paid to benefits in HBA, it is also important to review the degree and duration of harm to the animal subject.  Some questions arises such as: can refinement be further refined by even more definition to the betterment of animal subjects and separate from the benefit side of HBAs? Or what if the intended degree of harm to which a lab animal will be subjected cannot exceed the unintended pain or distress (”harm”) experienced by others under applicable circumstances like human or animal patients with equivalent disease or injury?. To which such an upper limit could be called “maximum harm equivalence”. And if staying within the max harm permitted, animal subjects could be provided supportive care as close as practical to supportive care given to patients with corresponding affliction.

A good example is animal research on Ebola virus. To which earlier outbreaks are almost always fatal to humans and as such to replicate the disease accurately, NHP were used and inoculated lethal dose of virus to study the course of disease and evaluate candidate vaccines and antiviral drug treatments under realistic conditions. This approach doomed many monkeys to death but 2013-2016 outbreaks case fatality with supportive care ranged 40-60% as compared to previous outbreaks of 80-90%.

We can presume that future Refinement in Ebola research like using non-lethal doses and supportive care to animals models of Ebola  can be done however in reality and sadly, Ebola research still involves high lethality and omits supportive care of a kind to NHPs. As aside, handling animals in BSL-4 is very difficult and must be safe for both animals care providers and scientists.

So, could a more defined refinement, under the principle of “maximum harm equivalence” and buttressed by human patient data, swing this animal model to a less harmful and more clinically relevant experimental design? Or are there other humane concepts besides “maximum harm equivalence” for limiting animal pain or distress, regardless of a projects possible scientific or medical benefit , may work better?

Summary: Despite the popularity and codification of HBAs for ethical review of animal research, they can still lead to poor outcomes if performed without regard to the false premise the represent, “that the benefits from research can and should be predictable and useful before approval can be granted.”

Several scenarios were described in which HBAs may enhance or impede medical and social progress, ending with expanded paradigm for refinement that would cap lab animal pain and distress separate from beneficial outcome from harmful experimentation. So therefore, critical review of methods, language, and consequences with an eye towards continuous improvement, must and should be encouraged frequently.

**Tannebaum. The Pursuit and Advancement of Knowledge as a Justification for the Use of Animals in Research, pp. 347-365**

Jennifer Asher, jennasher2@gmail.com

ILAR 2019, 60(3), 347-365

The Pursuit and Advancement of Knowledge as a Justification for the Use of Animals in Research

Tannenbaum, J

Domain 5: Regulatory responsibilities

Summary:

This article explores the rationale that the pursuit of knowledge is an ethically sound justification for the use of animals in research, irrespective of potential benefits. This concept applies strongly, but not solely, to basic research. The definition(s) of knowledge is/are discussed as well as categorizing factual vs. experiential knowledge, the former being hard facts and the latter pertaining to the human understanding of those facts. In the current system of evaluating animal studies, factual knowledge is the basis for assigning value/worth to a project and experiential value is often not explored. Two gaps noted in ethical evaluation include the merit of contemplation of the knowledge as well as any intellectual faculties and skills gained via the process of conducting the research.

Supporters of animal research often fall back on what the author terms the “spin-off argument,” which is defending basic research projects by arguing that they will likely develop into medical advancements (spin-offs) in the future. The author argues that this is unnecessary because the pursuit of knowledge alone is justification for many experiments involving animals. The spinoff argument has influenced many ethical assessment schemes in the US, at the level of the NIH/funding source as well as the IACUC level.

The author explores the value of “the lifestyle of science” to those conducting research. This includes the experiences and emotions of the scientists, both positive and negative, and the pleasures involved in the advancement of knowledge. The intrinsic value of these pleasures plus the fact that it is a distinctly human quality to experience pleasure by expanding knowledge are both discussed. These pleasures start with the researcher performing the study, but are shared amongst colleagues in the scientific community, newer generations of scientists in the field via teaching, and non-scientists who read about the studies to expand their own understanding. It is acknowledged that developing a way to assign value to these intangibles in order to use them to assess ethics of an animal study is a tall order, but should be attempted by the scientific community.

Tannenbaum takes a hard left turn and discusses the “carnivore baseline principle” (CBP), which is the argument that is it inconsistent and anti-intellectual for a society to be comfortable with killing billions of animals for the pleasure of food consumption, but not for the pleasure of the gain of knowledge. Points made include better living conditions and methods of euthanasia for research animals vs. food animals as well as the estimation that only 8% of research animals experience pain (beyond momentary) or distress. This includes the best sentence in the article: “Satisfaction at discovering or contemplating something that makes even a minor contribution to the body of scientific knowledge will likely be more valuable, and last longer, than the pleasures of eating even an artfully prepared frankfurter.” Improvements in how food animals are housed and treated, and how these things would be achieved, does not affect the plausibility of the CBP.

Questions:

1.     What is the CBP?

2.     True/False: It is estimated that 30% of research animals experience serious pain or distress.

3.     What is the spin-off argument?

4.     How many times does the author use the word “frankfurter” in the article?

Answers:

1.     Carnivore baseline principle

2.     False (8%)

3.     defending basic research projects by arguing that they will likely develop into medical advancements in the future

4.     3

**Turner. Moving Beyond the Absence of Pain and Distress: Focusing on Positive Animal Welfare, pp. 366-372**

Domain3: Research; Domain 4: Animal Care; and Domain 5: Regulatory Responsibilities

SUMMARY: The moral and ethical imperatives that are considered fundaments to achieve high standards in the care and use of animals in biomedical research are not only increasingly seen within the worldwide research community but are more extensively recognized at a wider level, considering the high value that society gives to the acceptance of animal sentience and the recognition of strong human-animal bonds and interdependencies.

There has been a shift in how society values animals, with a strong interest and will in promoting positive welfare, not only seen as just the physical state of the animal or the presence of negative affective states but rather as a wider presence of different states. This should take into account the emotional life of an animal, which is supported by a complex neurobiological system, allowing affective experiences of both positive and negative valence.

This paper has the aim to help defining positive animal welfare in the work with laboratory animals and shares some inputs to better understand how the research community can achieve positive welfare states for animals.

If, on one side, the ethical imperatives of sentience and responsible science are considered of paramount importance to ensure that research animals have a good welfare, on the other side, the author emphasizes how the absence of negative affective states *cannot* be used as a surrogate marker for positive animal welfare and underlines the importance of developing specific measures to evaluate positive affective states in research animals.

Some examples of possible species-specific measures of positive affective states have been proposed and include some behaviours that can be measured in laboratory rodents:

play behaviour, nonsexual affiliated behaviour, nest-building and burrowing activities, facial indicators of positive emotions, the use of vocalizations to recognize positive emotions, measuring cognitive bias and assessments of quality of life.

Despite the presence of such positive welfare indicators, it still appears to be challenging to implement these measures today, considering some practical constrains which are determined, for example, by the animal model and /or the experimental design and the need to add scientific reproducibility, quality and precision at the same time.

According to the author, a critical point is represented by the commitment to a more robust and comprehensive animal behavioural management programs within vivaria, with focus on appropriate housing and husbandry, social needs of species, food resources, respectful animal handling practices, a program to habituate and train animals to better prepare them for studies, exercise opportunities and a positive humane interaction.

According to the paper, if it is important to state that these aspects are directly related to the concept of *refinement*, at the same time, some key factors as minimizing animal stress and improving handling and cooperation with procedures should be applied more consistently to obtain better results; applying refinements more consistently may indeed allow the operational focus to shift from minimizing harms to optimizing positive welfare.

Additionally, conducting periodic animal welfare assessments, different from daily morbidity and mortality checks may allow the research community (veterinarians, researchers, animal technicians, others) to actively and objectively assess the welfare of research animals rather than assume that welfare of animals is adequate following initial protocol review.

QUESTION

1. What is sentience and is it possible to relate the concept of sentience to animals?

ANSWER

1. Sentience is the capacity of subjectively feel or experience an array of sensory inputs, which are processed by a nervous system into outputs of sensations, emotions, decisions, about appropriate responses, communication with others and generations of goal – directed behaviours (*Mellor DJ. Welfare -aligned sentience: enhances capacities to experience, interact, anticipate, choose and survive. Anim. 2019; 9: pii*:E440)

By definition sentience implies a conscious state and using this definition one should conclude that at least all vertebrate animals (perhaps also many invertebrate animals) are sentient.

**Makowska and Weary. A Good Life for Laboratory Rodents?, pp. 373-388**

Domain 4: Animal Care, K1. Species-specific husbandry and K2. Environmental enrichment, K8. Housing systems

SUMMARY: When using animals for research, ethicists argue that animals should be spared “unnecessary harm, pain or distress.”  In reality, that might equate to basic animal welfare needs such as food, water, shelter, freedom from disease, and treatment for veterinary conditions. Makowska and Weary argue that there should be a higher standard for research animal care (“a good life”) because it is better for reproducibility and allows for justification to stakeholders why research should get the privilege of using animals in research.   The authors describe their vision of a good life for lab animals (with a focus on rodents due to their importance in research, teaching and training). This paper focuses on the minimum daily living conditions to be met when using rodents in research.  Good animal welfare involves biological functioning, affective states and natural living. The authors argue that a good life for rodents would allow for expression of natural behaviors and engagement with their environment and that changes in the physical environment, interactions with humans and life beyond research may be considered. Considerations for bedding type (corn cob vs. aspen chip, for example), bedding depth, enrichment (shelter, nesting material), environmental complexity (e.g., adding dividers), cage complexity and segregation of space (e.g., tunnel caging systems, 2-tiered caging).  The authors argue that a good life would involve improved caging designs involving a larger size, more complexity, more naturalistic substrates and opportunities for natural behaviors such as digging/burrowing. A good life may also involve allowing access to play areas/playpens (large, structurally complex enclosures with intermittent access) for rodents as is done with larger species. In some studies, giving rodents access to free ranging environments may be beneficial to the animals and the research. Interactions with humans can also be stressful for rodents.  The authors describe several technique modifications that may be employed that can reduce stress with noticeable changes in physiologic parameters. Socialization is described in terms of acclimating rodents to handling.  Examples such as gentling and rat tickling are provided. Training rodents to cooperate (such as for husbandry, veterinary and research procedures) may have beneficial effects on animal welfare in rodents as in other species. The authors argue that positive changes in various aspects of husbandry and research will benefit research rodents tremendously, but do mention that there are downsides such as more personnel needed, more time investment, more monetary allocation, but that animal welfare and staff morale would be improved outcomes.

QUESTIONS

1.  Makowska and Weary argue that all of the following are components of a “good life” for laboratory rodents EXCEPT

a.  Improved bedding options

b.  Cage complexity

c. Improved handling and restraint

d.   Exposure to other species in a natural environment

e.  Socialization

2.  True/false:  Makowska and Weary, 2019 argue that researchers are ethically responsible to improve the life of laboratory rodents, but that there are limitations and potential downsides such as time investment for planning and caretaking, requirement for additional space and personnel, and increased cost for husbandry supplies/equipment.

ANSWERS

1.       d

2.       T

The authors do not bring up space issues, biosecurity issues and impact on husbandry waste management and cage washing needs of complex environments, but those would be other discussion points to consider as downsides/limitations.

**Schapiro et al. Behavioral Management is a Key Component of Ethical Research, pp. 389-396**

Domain 4; TT4.2

SUMMARY: Research projects can be considered ethical if they 1 involve animals with high welfare, 2 provide data that are reliable and valid, 3 involve appropriate numbers of subjects, and 4 involve animals that are appropriate models.  Behavioral management’s primary goal is to provide captive research animals with opportunities to perform normal, species-typical behaviors.  Two approaches to do this are 1 providing opportunities for the animals to perform behaviors that comprise species-typical repertoire and/or 2 providing opportunities for the animals to perform a subset of species-typical repertoire at species-appropriate rates.  For example, nest building species should be provided with nesting material.  One difficulty is that we are unable to truly understand their perceptual worlds and what they perceive as beneficial, neutral, or aversive. Animals behaving abnormally more likely provide data that is not valid.  Abnormal behaviors are defined as those not observed under natural circumstances or normal behaviors that are performed at abnormal rates or frequencies.  Behavioral management strategies are best utilized in the prevention of abnormal behavior patterns, rather than curing abnormal behaviors.  One of the best ways to assess welfare is systematic observation using well-defined sampling techniques.  Successful breeding, good parenting, appropriate weight, absence of wounds, injuries and/or illness suggest adequate welfare.  Captive animals generally have little control over their environments; well-designed management programs provide research animals with opportunities to use their sensory/perceptual and cognitive capabilities to make meaningful choices.  For example, nonhuman primates can be given the opportunity to choose the medication they prefer for alleviation of arthritis symptoms.  Three ways management can provide research animals with species-typical behavior are physical environmental design, composition of social environment and refinements to care procedures.  For social environment, it is important to empirically define the most effective densities and social group compositions.  There are many components of the physical environment that can be simulated, such as 1 substrate, 2 3-D environments that allow for climbing, 3 apparatus that encourage play, exploring or exercise for food or other resources, and 4 opportunities that differ in sensory experiences (smell, light, sound, etc.).  Captive environments should be designed so animals can move, hide, exercise, feed, eliminate, and rest in ways that are typical of the species in the wild.  Quality of space is more important than quantity of space.

Controlling environments so that there is a reduction in interindividual behavioral variation is referred to as a reduction error variance.  This leads to better results with fewer subjects being required.  Refinements in behavioral management, such as training subjects for voluntary venipuncture enhances the reliability of data and can lead to reduction in the number of subjects.  Human convenience also needs to be balanced with animal behavioral needs.  For example, mice don’t eat pellets that are located within reach, but it would be impossible for small caches of seeds be provided to every rodent cage all night long to simulate night foraging behavior of wild mice.  Behavioral management relies on refinements, such as providing foraging opportunities.

QUESTIONS

1. What is a difficulty we currently have in understanding an animal’s perceptual world?
2. What is one of the best ways to assess behavioral welfare and what assessments are considered adequate welfare?
3. What components of the physical environment can be simulated to provide species typical behaviors?
4. Differences in interindividual behavior is also called?

ANSWERS

1. We are unable to know what animals truly find beneficial, neutral, or aversive in their environments.
2. One of the best ways to assess welfare is systematic observation using well-defined sampling techniques.  Successful breeding, good parenting, appropriate weight, absence of wounds, injuries and/or illness suggest adequate welfare.
3. 1 substrate, 2 3-D environments that allow for climbing, 3 apparatus that encourage play, exploring or exercise for food or other resources, and 4 opportunities that differ in sensory experiences (smell, light, sound, etc.)
4. Error variance

**Fenton. Holding Animal-Based Research to Our Highest Ethical Standards: Re-seeing Two Emergent Laboratory Practices and the Ethical Significance of Research Animal Dissent, pp. 397-403**

Domain 6: Education; K3 - Societal issues involving use of animals, philosophy and ethics of animal use

SUMMARY: The article argues from an ethical standpoint that if animal-based research should be held to the highest ethical standards, then it should follow that positive reinforcement training (PRT) and rehoming of animals when euthanasia is not required in a protocol should be mandatory on ethical grounds. The author further makes an argument that "personhood" may be something that extends to other species such as nonhuman primates, dogs, cats, mice, rats, some birds, and perhaps some fish, as our highest ethical standards in human bioethics include references to personhood. This is not to say that these animal research subjects have the same rights as humans do, but any individual regardless of species should enjoy moral equality with us as humans. This requires use to direct compassion and protections to animals. Rather than using the term personhood, the author suggests saying "respect for intentional agents" when referring to animal research subjects. Intentional agents refers to "those sentient individuals capable of learning from their experiences and forming goals that they effectively act to satisfy."

Two emergent practices are understood as animal welfare measures to reduce unnecessary stress, and those are PRT and rehoming. PRT has the added benefit of impacting animal attendant welfare positively as the caretaker bonds with the animal he or she is working with. PRT allows intentional agents to choose whether or not to cooperate in a PRT session, and is therefore noncoercive. Rehoming allows intentional agents the chance to be in a setting without standard laboratory stressors (handling, loud mechanical noises, stacked cages, proximity to distressed conspecifics). Rehoming may also be beneficial to care staff who may find it difficult to euthanize healthy animals. The author argues that "affirmations of respectful treatment of research animals do not seem compatible with unnecessary euthanasia." If the animals can live the remainder of their lives in a sanctuary or as a pet, then this is compatible with respect for intentional agents.

The author lastly argues that signs of sustained dissent  when a procedure is distressing, such as attempts to withdraw or escape, should be respected. This respect for sustained dissent minimizes harm to the animals, which is always our goal in animal research. If we ignore sustained dissent and the power of PRT and rehoming, this comes at the cost of abandoning our claim to the moral legitimacy of the scientific use of animals.

QUESTIONS

1. What are intentional agents?

2. What is sustained dissent?

ANSWERS

1. Sentient individuals capable of learning from their experiences and forming goals that they effectively act to satisfy.

2. A level of decisional authority that does not require sophisticated or complex awareness; it is enough that a procedure is distressing or that the relevant individual does not want to cooperate, evidenced by attempts to withdraw or escape.

**Olsson et al. From Unpleasant to Unbearable – Why and How to Implement an Upper Limit to Pain and Other Forms of Suffering in Research with Animals, pp. 404-414**

Domain 2: Management of Pain and Distress

SUMMARY: This paper introduces the concept that there are strong moral and scientific reasons to favour an absolute ban on animal experiments resulting in severe suffering. Severe suffering occurs when negative experiences (such as pain or disease) are accompanied by a loss of control, lack of social support (in social animals) and/or fear and anxiety. Severe suffering “takes over” and fundamentally changes an animal’s life, and has a limited capacity for distraction/compensatory pleasure. Normal function cannot be maintained, and recovery becomes impossible even if the external or internal event improves. Severe suffering may be best measured by depressive-like states rather than focusing on conventional stress (e.g., cortisol) or non-specific welfare indicators. If banned, scientists will likely find alternative ways to achieve their aims without severe animal suffering. For example, severe suffering can be reduced or ameliorated through the use of surrogate endpoints (e.g., decreased CD4+ T-cells or increased blood HIV RNA in AIDS models), or through the use of adequate supportive care to better mimic the real human clinical setting. The authors argue that the proposed regulatory ban be supported *in practice* by all 3 major ethical perspectives on animal use in research: 1) animal rights, 2) deontological, and 3) consequentialist; in all perspectives, the ends cannot adequately justify the means.

QUESTIONS

1.  Which regulatory/policy/standards document states that “When included in an animal efficacy study, supportive care ideally should reflect the intended conditions of use of the investigational drug. It also should reflect the intended types of medical intervention and the timing of the availability of medical intervention expected in the human clinical or incident setting.”?

a.   GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

b.  The IACUC Handbook

c.   Animal Welfare Regulations

d.  Product Development Under the Animal Rule – Guidance for Industry

2.  Which of the following are considered in USDA pain and distress definition of categories D and E?

a.  Duration of pain or distress

b.   Severity of pain or distress

c.    Whether or not pain or distress is relieved

d.   All of the above

ANSWERS

1.  d

2.   c

**Walker. Virtue Ethics and Laboratory Animal Research, pp. 415-423**

Domain 6: Education

SUMMARY:Virtue ethics focuses on the role of a person's character in determining the moral value of actions, character traits, and transforms questions of welfare into questions about animal lives well lived. Basically, the perception and feelings of the person toward the animal and animal life is analyzed and assessed. Virtue ethics is less focused on questions of moral status and more focused on the development and maintenance of virtues of character, which is suggested to be lacking in animal research. Virtue ethics actually offers challenging alternatives to the primary focus on animal moral status and draws attention to issues beyond animal welfare. It places the central emphasis on the human character traits promoted or undermined by engagement in animal research.

Virtue ethics suggest that institutional shifts be implemented such that it fosters an environment in which such virtues can flourish as part of habituation into best research practices. Factors that can support the development of these virtues include mentorship by researchers with the right kinds of experiences, oversight mechanisms that require attention to translational value issues, and institutional support for scientists willing to make major shifts in their approach to animal research for translational value reasons.

Virtue ethics can be applied to 4 key issues in animal research: animal welfare, human-animal bonds, mentoring, and translational science value.

Rival philosophical theories of morality to virtue ethics are: consequentialist (primarily utilitarian) and deontological (primarily rights-based) which addresses questions about whether or when animal research is justified but less helpful in considering ethical issues internal to animal research. In general terms, utilitarian theories are concerned with sentient animals and their experiences. Rights-based theories focus fundamentally on whether animals have the moral status of having rights. Neither theory is primarily concerned with what a good life would actually look like for the animals in question.

QUESTIONS

1. What is the primary goal or philosophy of virtue ethics?

a.   The moral standing of the animals used in research and teaching

b.  The role of a person's character in determining the moral value of actions and traits toward animals used in animal research

c.  Ethical issues and moral justification of animals used in research

d.   The role of a person to use animals for research and the relative harm to them and potential for human (or other animal) benefit (risk vs benefit)

2. What are the 4 keys animal research issues presented in this paper in which virtue ethics can be applied to?

a. Animal welfare, animal-animal bonds, training, and translational science value

b.  Animal welfare, human-animal bonds, mentoring, and translational science value

c.  Animal welfare, communication, teaching and training, and translational science

d.  Animal welfare, veterinary and support staff communication, mentoring, and teaching

ANSWERS

1. b

2. b

**Shriver and John. Neuroethics and Animals: Report and Recommendations From the University of Pennsylvania Animal Research Neuroethics Workshop, pp. 424-433**

Domain 3:Research

SUMMARY:This article summarizes the perspectives of two attendees following the “Neuroethics of Animal Research” workshop that was hosted at the University of Pennsylvania in June 2016. This workshop discussed the poor translatability from animal models to human clinical outcomes. The authors suggest that this may be due to inappropriate animal models. Pain tests most used in animals involve spinally mediated reactions (not dependent on brain activation) and focus on acute pain while most clinically significant challenges in humans involve chronic pain with sensory and affective components. Conditioned place preference tests and facial grimace scores are listed as two models of pain that may be more applicable for evaluating pain in animals and more closely correspond to the humane condition

New models of pain in animals are validated using the original pain models and thus limits advancements to developing models that may more accurately represent the human condition. This is also the case for new models of toxicology (such as brains-on-a-chip) that are required by the FDA to be validated against previously used imperfect animal models. Symptoms of psychiatric disease in humans such as hallucinations, delusions, sadness and guilt cannot be easily ascertained in animals and may lead to poor model translatability. Additionally, the authors point out that researchers studying the disease may not be as well versed in the clinical picture as human physicians so they may miss cues that the model is not recapitulating human disease and homogeneity among animal research subjects does not reflect the diverse and heterogenous human population. Pharmaceutical companies are moving away from less translatable animal models faster than academic researchers. They suggest this is caused by financial incentives for the pharmaceutical companies to produce effective treatments and financial de-incentivization for academic researchers who rely on grants that are more likely to be funded if they use previously published animal models.

This workshop also discussed ethical issues surrounding the use of brain-machine interfaces (BMI) technology by the US military and a commercial product “Roboroach”. The authors argue that BMI technology used in these situations would allow animal’s movements to be controlled by outside forces which raises moral concerns about the loss of liberty and autonomy and could lead to general disregard for animal welfare. Human-nonhuman chimeras are banned by the NIH but there are no regulations on animal-animal chimeras. The question was raised as to what ethical standards should be applied after neural cells were combined from 2 different organisms. The authors suggested that we should not apply blanket ethical rules but should assess the moral significance of each alteration. The authors felt that there is unclear understanding of what neural attributes would make non-human animals worthy of “personhood” and did not feel that this discussion should be used to guide current research guidelines.

The authors suggested the following 4 things: harm-benefit analysis should be performed, guidelines should be developed for animal models of psychiatric conditions, greater funding should be allocated for in-vitro model development, and research should be conducted on the welfare concerns regarding external control of animals.

QUESTIONS

1. Which of the following is not a test for pain used in rodents?
   1. Tail flick
   2. Hargreaves
   3. Running wheel
   4. Von Frey
2. Which of the following most accurately defines a chimera?
   1. Two organisms that differ in only one locus of their chromosome
   2. An organism containing a mixture of genetically different tissues
   3. The offspring produced by crossing two different inbred strains
   4. The offspring produced by backcrossing a locus of interest onto an inbred strain for 10 generations
3. Which of the following ethical theories is best represented in the harm-benefit analysis of animal research?
   1. Utilitarianism
   2. Deontology
   3. Consequentialism
   4. Eudaemonism

ANSWERS

1. c. Running wheel
2. b. An organism containing a mixture of genetically different tissues
3. a. Utilitarianism = consider the happiness it would bring to the maximum number of things (i.e. harms to nonhuman animals are outweighed by the potential benefits that would accrue to humans)

**Devolder et al. The Ethics of Creating and Using Human-Animal Chimeras, pp. 434-438**

Domain 6: Education

SUMMARY: There are many ethical concerns related to the development and research use of human-animal chimeras. Advances in stem-cell and gene-editing technology have propelled the field forward and scientists have been able to increase the prevalence of human-derived cells in animal hosts, from mice to pigs and sheep. Chimeras can be intraspecific, meaning all cells belong to the same species, or interspecific, meaning the chimera contains cells from at least 2 different species. Human-animal chimeras can include an animal or animal embryo containing human cells and a human or human embryo containing animal cells. This review focuses on chimeras that involve animals containing human cells, since this approach has been used extensively in biomedical research and is more likely to receive further attention in the near future. There are two main attractions to using human animal chimeras: 1) it allows for human cells and tissues to be studied in vivo without requiring experiments on humans; and 2) they provide better models of human cells /tissues than non-chimeric models. The majority of human-animal chimeras created to date involved inserting human cells into animals at post-embryonic stages of development, thus limiting the presence of the progeny of the human donor cells to the tissues into which they were introduced. If donor cells from an embryo or embryonic stem cells are introduced into another early embryo, the resulting chimera could have progeny of the donor cells in many different tissues. The 2005 Guidelines for Human Embryonic Stem Cell Research, published by the US National Academy of Sciences, recommends review by oversight committees for any research where human embryonic stem cells are introduced into animals at any stage of development, and specifically prohibit research in which human embryonic stem cells are introduced into nonhuman primate blastocysts, and the NIH does not fund any of this specific type of research.

The use of human cells to create genetically modified organisms can lead to questions about the moral status of human-animal chimeras, especially if they develop humanized cognitive capacities- do they possess human dignity, and if so, what are the ethical concerns with creating beings with human dignity that will knowingly be used and/or treated in a way that does not benefit their dignity (such as biomedical research)? What about the potential for human stem cells to contribute to the reproductive potential of a non-human host, or the ability of a human-animal chimera to produce human gametes? Could it undermine or detract from the inherent value of human gametes, and what of the appeal to intuitive moral responses (aka the “yuck factor”)? Alternatively, a non-human animal capable of producing human gametes could aid research in regenerative medicine while reducing the number of women needed to donate eggs for research (which has safety risks), while offering potential solutions to infertility in human patients. Many of the ethical concerns surrounding human-animal chimeras can be applied to the creation of animal-animal chimeras, especially if nonhuman primates are used.

QUESTIONS

1. The introduction of retinal cells from a fetal mouse into a blind adult mouse is an example of what kind of chimerism?

a. Interspecific

b. Intraspecific

c. Human-animal

2. True or False: The NIH funds research in which human embryonic stem cells are introduced into nonhuman primate blastocysts.

3. Which of the following is an advantage to using human-animal chimeras?

a. There are few, if any, ethical concerns.

b. They allow creation of human-animal hybrids capable of producing human gametocytes.

c. It allows for human cells and tissues to be studied in vivo without requiring experiments on humans.

d. There are no advantages, and the practice should be discontinued.

ANSWERS

1. b

2. False

3. c