

Principles of Animal Research Ethics



Tom L. Beauchamp & David DeGrazia

Principles of Animal Research Ethics

Principles of Animal Research Ethics

TOM L. BEAUCHAMP

and

DAVID DEGRAZIA

OXFORD
UNIVERSITY PRESS

OXFORD

UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.

© Oxford University Press 2020

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, without the prior permission in writing of Oxford University Press, or as expressly permitted by law, by license, or under terms agreed with the appropriate reproduction rights organization. Inquiries concerning reproduction outside the scope of the above should be sent to the Rights Department, Oxford University Press, at the address above.

You must not circulate this work in any other form
and you must impose this same condition on any acquirer.

CIP data is on file at the Library of Congress
ISBN 978-0-19-093912-0

1 3 5 7 9 8 6 4 2

Printed by Sheridan Books, Inc., United States of America

For Ruth Faden and Kathleen Smith for their invaluable support

Contents

Preface	ix
Preamble	1
Principles of Animal Research Ethics	5
<i>David DeGrazia and Tom L. Beauchamp</i>	
The Essential Place of Moral Justification	5
Principles of Social Benefit	6
The Principle of No Alternative Method	7
The Principle of Expected Net Benefit	8
The Principle of Sufficient Value to Justify Harm	9
Principles of Animal Welfare	11
The Principle of No Unnecessary Harm	12
The Principle of Basic Needs	14
The Principle of Upper Limits to Harm	16
The Crucial Role of Ethics Review Committees	18
Scientific Necessity as a Justification for Causing Harm	20
On <i>The Principles of Humane Experimental Technique</i>	21
Critical Commentary by Authorities on Animal Research Ethics	43
The Potential and Impacts of Practical Application of Beauchamp and DeGrazia's Six Principles	45
<i>Larry Carbone</i>	
Some Reflections on Primates in Research	61
<i>Frans B. M. de Waal</i>	
Putting the Ethical Principles into Practice	69
<i>Rebecca Dresser</i>	

The Mouse in the Room: The Critical Distinction Between Regulations and Ethics <i>Joseph P. Garner</i>	79
Compassion for Other Animals Beyond the Human Hierarchy of Concern <i>Brian Hare</i>	99
Commentary on the Beauchamp-DeGrazia Framework of Principles <i>Margaret S. Landi</i>	113
The Six Principles, Philosophy, and Applying Human Ethics to Animals <i>Julian Savulescu</i>	127
Biographical Information on the Authors and Commentators	147
Index	155

Preface

This book presents a framework of general principles of animal research ethics organized under headings that express the framework's core values. These principles should be found acceptable by representatives of both the animal research and the animal protection communities without sacrifice of their basic moral commitments. These two communities are not as clearly distinguishable by their beliefs as many commentators have suggested, and the individuals within each community are not monolithic in their commitments. Many codes of ethics formulated by professional societies such as those in veterinary medicine are available for professionals to consult, and government regulations are in place in almost every country in which animal research is conducted. However, no code or regulatory scheme presents a framework of general principles of animal research ethics together with an analysis of the principles' meaning and moral requirements.

For decades, the sole canonical text in animal research ethics has been William Russell and Rex Burch's *Principles of Humane Experimental Technique*, which appeared in 1959. This book established the so-called Three Rs: *replacing* sentient animals with other models where possible; *reducing* the number of animal subjects to what is needed for statistical adequacy; and *refining* techniques to reduce animal suffering. The Three-Rs conception represents an important advance in the promotion of animal welfare, but this framework does not feature general moral principles that display the core values at work in animal research ethics. In addition, the Three-Rs framework does not adequately address the costs and benefits of animal research to human beings or include a comprehensive program of protection for animal subjects.

On the Selection of Commentators. A distinctive feature of the present book is a large section containing critical commentary by prominent scholars and practitioners representing several disciplines. The authors of *Principles of Animal Research Ethics* selected the commentators on the basis of their expertise, excellence in published writings, diversity of background, fair-mindedness, and extensive experience in conducting or assessing animal research. Collectively, they represent the fields of veterinary medicine, biomedical research, biology, zoology, comparative psychology, primatology, law, bioethics, and philosophy. The authors deeply appreciate the contributions of these commentators, who have worked tirelessly to evaluate our framework of principles and to think constructively about practical uses of these principles.

The Order of Authors' Names. Beauchamp and DeGrazia regard themselves as equal contributors to this thoroughly collaborative work. However, they have agreed on the convention of listing Beauchamp's name first for the book as a whole and listing DeGrazia's name first for the centerpiece section that carries the title *Principles of Animal Research Ethics* in the Table of Contents and the text.

Declarations by the Authors. Beauchamp's work on this book was supported by the National Science Foundation under Grant No. 1058186. The opinions, findings, and conclusions or recommendations expressed in this work do not necessarily reflect the views of the National Science Foundation. DeGrazia's work on this project has been supported, in part, by intramural funds from the National Institutes of Health Clinical Center. The views expressed are the authors' own. They do not represent the position or policy of the National Science Foundation, the National Institutes of Health, or any other part of the U.S. federal government.

Preamble

Research involving animals has advanced since its inception without the aid of a framework of general moral principles. The need for such a framework might therefore be doubted, but several developments call for a reconsideration and reconstruction of animal research ethics. First, public concerns about animal welfare have increased substantially in recent decades and continue to increase. Second, the scientific study of animals has afforded a wealth of new insights into their behaviors, mental lives, and basic needs. Third, animal ethics emerged in the last quarter of the twentieth century as an important field of interdisciplinary scholarship and has expanded for several decades, frequently challenging traditional ways of thinking about animals' moral status and human responsibilities for their care and use.

Human research ethics has long benefited from general moral principles such as those in the *Belmont Report* of the U.S. National Commission for the Protection of Human Subjects, but no comparable framework of principles has been available to assist investigators, research institutions, and government agencies in assessing the justifiability of uses of animals in research. A well-conceived framework of general principles that exhibits the core values of animal research ethics should facilitate the ethical examination, guidance, and oversight of animal research.

We consider it unfortunate that the ethics of animal research is often viewed through only one of two perspectives that are widely perceived as conflicting and irreconcilable.

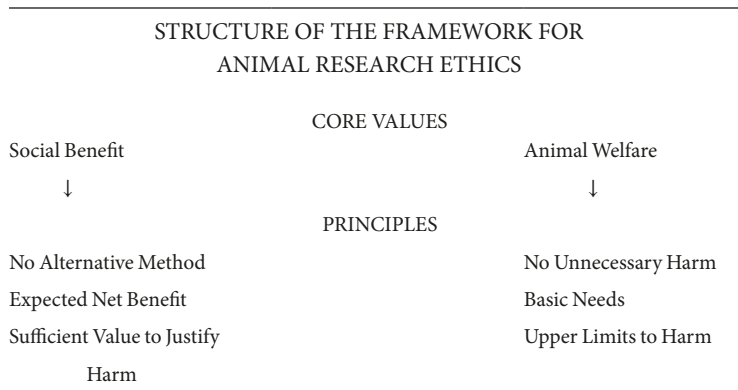
First, from the perspective of many in (and beyond) the biomedical and behavioral research communities, animal research is crucial to progress because animal models provide valuable insights into human biology and behavior while freeing human subjects from unnecessary research risks. Animals are frequently harmed in research, but human interests have a greater moral significance than animals' interests in avoiding harm. The harms caused to animal subjects are justified, from this perspective, by the procurement of vital scientific information and therapeutic benefits and by the superior moral status, dignity, or worth of human beings. The primary guidepost for ethical evaluation of animal research protocols is the framework of the "Three Rs": replacement of animals with nonanimal resources; reduction in the number of animals used; and refinement of procedures, housing conditions, and the like to reduce animal pain, distress, and suffering.

Second, from the perspective of persons who seek improved protections for animals, the justifiability of invasive animal research is often open to question, and hypotheses regarding its scientific value, therapeutic value, and promise of social benefit must be supported by rigorous evidence and argument. The moral status of animals also sets limits on the justified uses of animals in the pursuit of progress in the biomedical and behavioral sciences. Animals in research, like humans, have welfare interests that play a significant role in determining the content of researchers' obligations to treat animal subjects appropriately. Although consensus is lacking on the best set of guidelines for evaluating animal research, this second perspective typically regards the Three-Rs framework as insufficiently responsive to the moral status of research animals and as lacking a comprehensive program of animal protection.

It might seem futile to seek substantial common ground between these two perspectives on animal research ethics. We believe, however, that reasonable representatives of the animal research and animal protection communities can and should converge on three pivotal claims: (1) sentient animals have moral status and therefore

are not merely tools of research; (2) the only possible justification for (nontherapeutically) harming animals with moral status, including animal research subjects, is the prospect of substantial and otherwise unattainable social benefits; and (3) any permissible harming of animals in research is limited by considerations of animal welfare. In brief, sentient animals matter morally, and the core values of animal research ethics are *social benefit* and *animal welfare*. These values of social benefit and animal welfare are already embraced in animal research regulation, practice, and philosophy even if the implications of these values are not always adequately appreciated in policy and practice.

Proceeding from these two commonly held values, we construct our framework of six principles, which we believe can be accepted by open-minded representatives of the animal research and animal protection communities without sacrifice of their basic commitments. To anticipate our later discussion of the principles, here is a diagram of the connections between the two core values and the six principles that constitute the normative structure of our framework.



Although other moral values or principles such as *respect for animals* and *justice as fairness* arguably deserve a place in animal research ethics, the values underlying the current framework have been deliberately limited to those that every reasonable individual can be expected to endorse.

The overall goal of this book is the articulation of a framework of principles that is philosophically sound, useful for persons engaged in research involving animals, and capable of promoting consensus about the core values of animal research ethics. This framework is compatible with the Three-Rs framework but calls for a more thoroughgoing assessment of relevant costs, risks, and benefits and a more comprehensive conception of animal-subjects protection. These principles also indicate how the socially beneficial involvement of animals in research can be made compatible with their having decent lives, as all can agree is an estimable goal.

Tom L. Beauchamp,
Washington, DC, and Chilmark, Massachusetts

David DeGrazia,
Bethesda, Maryland, and Washington, DC

Principles of Animal Research Ethics

David DeGrazia and Tom L. Beauchamp

The six general principles articulated in this document provide a framework for the moral evaluation of practices, policies, and protocols in research involving captive animal subjects.¹ This framework is fashioned expressly for animal science in which the welfare of animal subjects is dependent on human investigators, administrators, and their personnel. A moral framework appropriate for research involving unconfined, wild animals would require modification of the present approach.

The Essential Place of Moral Justification

Three features of scientific research involving animals in controlled environments (hereafter “animal research”) call for justification by individuals and institutions conducting animal studies.² First, this research typically causes harm to its subjects. Harm can occur from experimental procedures, housing conditions, handling, stressful transportation, and the like. Second, animal subjects are incapable of providing informed consent for involvement in research studies. Third, nontherapeutic animal research ordinarily offers no prospect of a medical or veterinary benefit to its subjects.

These three features amount to harming animal subjects without their consent for nontherapeutic purposes, a paradigm of unethical research when human subjects are involved. When animals are the subjects, these features entail that the research bears a burden

of moral justification. From the premise that scientific research provides valuable knowledge, it does not follow that any particular research protocol is warranted. Investigators and other accountable parties have professional responsibilities to provide explicit moral and scientific justifications for their proposed uses of animals, for the choice of animal model, and for the number of animals used. Members of animal care and use committees likewise have a responsibility to evaluate whether the justifications offered by investigators are adequate.

This framework of six principles pertains only to research with animals that includes the aforementioned three features.³

Principles of Social Benefit

Each of the six principles presents a *necessary condition* of morally justified research, meaning that animal studies should not be conducted if the requirements of even one of these principles are not satisfied. Whether satisfaction of the demands of all six principles is also a *sufficient condition* of morally justified research is a difficult moral question not addressed here, but the importance of these principles as statements of necessary conditions is a point on which all should be able to agree.⁴

The first three principles pertain to the social benefits of research and the relationship of those benefits to its costs and risks of harm. These three principles are briefly stated here and will be explained in detail thereafter:

- (1) **The Principle of No Alternative Method:** Use of animal subjects must be the sole ethically acceptable way to address a research problem whose solution offers the prospect of a social benefit. (A claim that no ethically acceptable alternative method is available should be demonstrated on carefully reasoned grounds in protocols.)

- (2) **The Principle of Expected Net Benefit:** The prospect of social benefit from a research study must outweigh its expected costs and risks to human beings. (The basis for expecting a net benefit and the projected costs and risks should be demonstrated on carefully reasoned grounds in protocols.)
- (3) **The Principle of Sufficient Value to Justify Harm:** The prospect of a net benefit for human society from a research study must be sufficiently valuable to justify expected harms to animal subjects. (The basis for judgments of sufficient value to justify harm should be stated in protocols.)

In the explication of these principles that follows, the term “costs” refers to projected financial costs and opportunity costs (that is, potential benefits such as a new therapy that are not pursued as a result of a particular decision), and the term “risks” refers to possibilities of harm to humans. Terms such as “imposed harms” and “anticipated harms” refer to harms to nonhuman animals.

The Principle of No Alternative Method states that the use of animal subjects is justified only if the knowledge and social benefits pursued in a research study are not ethically obtainable through alternative research methods that do not use live animals.⁵ Animals should not be harmed if suitable alternative models are available to achieve the goals of the research. Sometimes it is possible to address a research question rigorously and with ethical justification by proceeding directly to human trials rather than conducting animal studies beforehand. At other times doing so poses excessive risks to human subjects, which is one reason the principle of no alternative method states that the knowledge sought must not be *ethically* obtainable using alternative methods. When human subjects cannot be used justifiably, a proposed animal study must be determined to offer the only methodologically sound means to scientific goals. If, for example, methods that use human tissues, cell cultures, or computer models are sufficient, sentient animals must not be used.

The Principle of Expected Net Benefit states that the prospect of a social benefit must exceed the expected costs and risks to human beings. Estimations of the prospect of benefit should take into account both the magnitude of the benefit if achieved and the no less important matter of the likelihood of achieving it. An estimation of this likelihood might be based on the frequency with which comparable research has previously yielded or failed to yield benefits. Estimations by investigators and review committees of the prospect of benefit should state whether the benefits of *basic research* are counted as benefits in their evaluations. Basic research often has the benefit of producing new knowledge, sometimes by serendipity, but much basic research does not produce biomedical benefits or even significant gains in knowledge. In general it is difficult to reach accurate prospective assessments of the value of new knowledge in basic science.

Animal testing—the use of animal models in studies of medicines, medical technologies, novel surgeries, and the like—is a sector of animal research in which the possibility of inaccurate conclusions is relevant to determinations of the costs and risks of the research. Weakness in an animal model increases the likelihood of one or more of the following errors: (1) *false toxicity negatives*, in which interventions appear safe in animal subjects yet would be harmful in humans (creating a risk of harm to human subjects); (2) *false toxicity positives*, in which interventions appear unsafe in animal subjects, yet would be safe for humans (creating a possible opportunity cost); (3) *false efficacy negatives*, in which interventions fail to work in animal subjects but would work in humans (creating a possible opportunity cost); and (4) *false efficacy positives*, in which interventions work in animal subjects but would be ineffective in humans (imposing financial costs without social benefit).⁶

As the likelihood increases that a given animal study will fall into one of these categories of error, the costs or risks of conducting the study stand to increase. In view of both the prospect of benefit and the estimated costs and risks, an ethically necessary condition for

conducting research is that the prospect of benefit must exceed total anticipated costs and risks to human beings. If investigators do not present a credible case that the prospect of benefit exceeds expected costs and risks, inadequate grounds exist to support a claim that the research is justified and worth pursuing even from a standpoint that considers only human interests—that is, a standpoint that does not take account of the interests of animal subjects. The interests of animals are considered in the next subsection on the principle of sufficient value to justify harm and in the section that follows on the three principles of animal welfare.

The Principle of Sufficient Value to Justify Harm, the third principle of social benefit, is essential to the framework of principles because satisfying the two principles of no alternative method and expected net benefit is not sufficient for moral justification. If animals did not matter morally, a reasonable expectation that a particular animal study would yield a net benefit for human beings and constituted the only way to procure that benefit would make the ethical justification of the study straightforward. But *sentient* animals, who are capable of pleasant or unpleasant experiences, do matter morally.⁷ They have moral status, which is why animal welfare concerns have long been central in animal research ethics.⁸ (Hereafter, unless otherwise specified, the term “animals” refers exclusively to sentient animals.)

When a study will impose harm on animal subjects, institutions, investigators, and review committees must judge how much prospective net benefit to society counts as sufficiently valuable to justify anticipated harms to the research subjects. It is understandable that disagreement may arise when multiple evaluators are making these judgments. This disagreement may be rooted in different assessments of animals’ *level* of moral status. Before we examine this type of disagreement, the concept of moral status and the basis for the claim that animals have moral status need clarification.

To say that animals have moral status is to say that they count morally in their own right⁹ (not merely as resources for others’

benefit) and that ethical decision-making must take into consideration their interests in avoiding harm.¹⁰ This moral proposition is supported by commonsense judgments that research animals should not be harmed for inconsequential reasons and by prevailing regulations, guidelines, and oversight provisions that protect animal welfare. Virtually every country and every major scientific association have supported guidelines that reduce or limit the harming of animals in biomedical research.

Academic writers in animal ethics almost uniformly hold that animals have moral status and support their claims with arguments. One type of argument begins with the premise that cruelty to animals is morally wrong and shows that any adequate account of cruelty's wrongness acknowledges the moral status of its victims. Another type of argument begins with the premise that suffering is bad in itself and maintains that the badness and its moral importance do not depend on a subject's species. A third type of argument begins with the consensus view that human beings, including those with profound cognitive disabilities, have moral status and posits that the most plausible reason for their meriting this status is that they have welfare interests, a basis for moral status that extends to animals.¹¹

Although it is well-established that animals have some degree of moral status, the *level* of their moral status is a difficult matter of reasonable dispute. Some believe that animals have a sufficiently high level that no amount of expected net benefit justifies harming them in nontherapeutic research. From this perspective, the moral status of animals warrants a prohibition on their use in research as a means to benefit humanity. Those who believe that animals' moral status does not warrant a categorical prohibition judge that some amount of expected net benefit is sufficient to justify involving animals.¹²

Despite understandable disagreement regarding how much expected net benefit is sufficient to justify anticipated harms to animal subjects, all who appreciate that animals matter morally can accept the principle of sufficient value to justify harm. Issues regarding the

level or levels of moral status of animals used in research do not challenge the moral importance of this third general principle.

Principles of Animal Welfare

Meeting the demands of the three principles of social benefit is not sufficient to justify harming animal subjects in research, because the demands of three additional principles must also be satisfied. These principles pertain to animal welfare.

All sentient animals possess a subjective quality of life—or experiential welfare—meaning that their lives can go well or badly in the felt quality of their experiences. Levels of welfare vary from exceptionally high to exceedingly low. Some confusion appears in the literature on animal research ethics because the term “welfare,” like its near synonym “well-being,” often, if not always, carries a connotation of a high level of welfare, including good health, absence of suffering, satisfaction of psychological and social needs, and adequate nutrition, hydration, and shelter. (See further the subsection titled “The Principle of Basic Needs.”)

The moral importance of the welfare of animal subjects is recognized globally in laws and codes. Virtually all nations and major scientific associations involved in animal research recognize that animals have a welfare that must be protected.¹³ They acknowledge that it is inhumane to treat sentient creatures merely as means to the ends of science without proper attention to their basic needs and welfare interests.¹⁴ Investigators and other responsible parties—including laboratory assistants, sponsors, suppliers, veterinarians, housing and feeding aides, transportation officials, and members of care and use committees—are obligated to acknowledge the moral importance of animal welfare in their actions. They must assess and justify harms they impose on, or intentionally allow to happen to, animal research subjects, just as investigators are obligated to justify risks taken with human research subjects.

The three general principles of animal welfare are stated here and are explained in detail later:

- (1) **The Principle of No Unnecessary Harm:**¹⁵ Animal subjects must not be harmed unless a particular harm is necessary for and morally justified by scientific purposes.
- (2) **The Principle of Basic Needs:** Animal subjects' basic needs must be met in the conduct of studies unless failure to meet specific basic needs is necessary for and morally justified by scientific purposes.
- (3) **The Principle of Upper Limits to Harm:** Animal subjects must not be caused to endure severe suffering for a lengthy period of time.¹⁶ In rare, extraordinary cases, exceptions may be warranted if the research is necessary for and morally justified by critically important social and scientific purposes.

In these three principles of animal welfare (and elsewhere below) the words “morally justified by scientific purposes” do not mean merely “scientifically justified.” These words mean *morally* justified by the social benefits of scientific research, without implying that scientific purposes can by themselves morally justify harming or failing to meet basic needs. The three principles of social benefit—as discussed in the preceding section—require evaluation of the social purposes of the research and, in particular, the magnitude of an anticipated social benefit and the likelihood of achieving it. The moral justification should be presented in a research protocol in which a statement of scientific justification may also be included. (See also the section “Scientific Necessity as a Justification for Causing Harm” below.)

The Principle of No Unnecessary Harm is grounded in commonsense ideas that causing harm tends to be morally wrong and that foreseeable instances of harming require a justification that shows the actions to be morally acceptable. Interventions and conditions that cause harm in the form of pain, distress, suffering,

or impairment of function in humans will have a similar effect on many other sentient animals, given their similarity to humans in susceptibility to aversive experiences and harms. As with humans, when harms have several sources—such as transportation, experimental procedures, and lack of food—they are additive in their impact on animal research subjects. The fact that the animals who experience these harms are nonhuman does not expunge the moral significance of the harming.

Animals should not be caused pain, distress, suffering, or the like in experimental procedures unless the harm is unavoidable because of morally justified scientific objectives that satisfy the principles of social benefit. Animal subjects also must not be harmed through negligence—for example, when careless handling or transport causes unnecessary fear, stress, discomfort, or injury. If proceeding with valuable animal studies is impossible without causing some harm, the principle of no unnecessary harm requires minimization of the harm consistent with sound scientific procedures and objectives.

The moral requirement that nonanimal alternatives be used when they suffice for the pursuit of methodologically sound scientific objectives is supported by both the present principle of no unnecessary harm and the principle of no alternative method.

In addition to prohibiting the causing of unnecessary harm to animal subjects and requiring that anticipated harms be justified, the principle of no unnecessary harm requires conscientious efforts to prevent the occurrence of unnecessary harmful conditions, that is, harmful conditions other than those justified as scientifically necessary. For example, the principle requires sanitary laboratory conditions and other appropriate steps to prevent the spread of disease through a population of animals. Preventive efforts should be made in experimental procedures, housing, handling, transport, and other interactions with animals.¹⁷

If unexpected harmful conditions develop, the principle of no unnecessary harm requires efforts to reduce or eliminate the harm.

For example, if animal subjects are harmed by a power outage that causes an interruption in essential air conditioning, the principle requires restoring air conditioning as soon as possible and providing any needed veterinary care. Risk assessment, risk management, and risk–benefit analysis are key tools in the prevention of harms in research.¹⁸

The Principle of Basic Needs requires investigators and caretakers to meet animal subjects' basic needs unless failure to meet one or more basic needs is an unavoidable consequence of, and morally justified by, scientific procedures in a well-designed protocol that satisfies the three principles of social benefit. A basic need is an especially important category of welfare interest. Satisfaction of basic needs is necessary for animals to have a minimally decent quality of life. Animals used in research have basic needs for minimal pain, avoidance of disease, and conditions that are conducive to good health, functioning, and experiential welfare. In the case of many species, basic needs include psychological and social needs.

This requirement to satisfy animal subjects' basic needs—with exceptions permitted only if morally justified by the social importance of scientific objectives—may seem overly demanding. It might seem morally sufficient to require only the avoidance of unnecessary harm. However, this assessment does not recognize that failure to meet subjects' basic needs constitutes a type of harm in the context of the special relationship between human personnel and animal subjects in controlled research environments. For example, a failure to feed animal subjects harms them, just as human parents harm their infants if they fail to feed them. The deliberate creation of situations in which humans have control over the care and use of animals, who are thereby rendered thoroughly dependent on their caretakers, generates role obligations on investigators and other responsible parties. Neglect of these obligations is moral, and often legal, wrongdoing.

Advances in modern science have deepened human knowledge of the basic needs of animals. A plausible catalogue of basic needs includes the following:

- Nutritious food and clean water
- Safe shelter
- Adequate stimulation, exercise, and opportunities for species-typical functioning
- Sufficient rest to maintain physical and (where applicable) mental health
- Veterinary care
- For social species, access to compatible conspecifics or social group members
- Freedom from significant experiential harms such as pain, distress, and suffering
- Freedom from disease, injury, and disability
- Freedom of movement with adequate space¹⁹

It is controversial whether the following is a basic need:

- Freedom from premature death

An animal's death is premature in the relevant sense if death occurs when the animal's life would be worth continuing, in which case euthanasia²⁰ would not be preferable for the animal's sake. No attempt is made in this framework of principles to decide whether avoiding premature death is a basic need, but this hypothesis presents a significant issue worthy of searching discussion during the ethical review of research studies.

Available evidence suggests that the class of sentient animals extends beyond the human species to include at least other mammalian species and birds. The preponderance of evidence arguably suggests that sentient animals include most vertebrate species and cephalopods. This hypothesis is consonant with the scope of

current animal research regulations in the United States and the European Union.²¹

Because sentient animals have an experiential welfare, they have an interest in avoiding pain, discomfort, distress, suffering, exhaustion, stress, and other unpleasant experiences. Moreover, the goal of protecting and enhancing the “psychological well-being of primates” has become of paramount importance in one region of animal research ethics,²² and this notion can be extended beyond primates. Animals with emotional capacities are subject to harms that include anxiety, suffering, depression, fear, sadness, boredom, and frustration. Social animals have an interest in species-typical forms of social functioning and may be psychologically harmed by the loss of close associates or family members. Psychological harm in research includes the sometimes hidden suffering that results from maternal separation, social isolation, sleep deprivation, cage confinement, stressful modes of transportation, and the like.

Neither the principle of no unnecessary harm nor the principle of basic needs establishes a ceiling on the level of permissible harm. A third welfare principle is needed for this purpose.

The Principle of Upper Limits to Harm prohibits a protocol design in which animal subjects are expected to endure severe, long-lasting suffering. The upper limit, or maximum, of allowable harm is exceeded whenever—as a matter of experimental procedures, housing conditions, or other controllable factors—animal subjects endure severe suffering that cannot be ameliorated by appropriate anesthesia, analgesia, sedatives, changes in living conditions, or the like and persists for a significant length of time. Euthanasia will in some cases either prevent the occurrence of severe suffering or limit its duration in a way that complies with the present principle.

Implementation of the standard of an upper limit requires investigators and animal care and use committees to develop operational criteria that specify what qualifies as severe suffering and what qualifies as an unacceptably lengthy period of time. Severity should be determined by the intensity and duration of the adverse events

suffered, which can sometimes be measured by appropriate quantitative tools. Reasonable estimates of the magnitude of severity are achievable even if the precision of these estimates is limited.

To facilitate understanding of the concept of an upper limit, policies will need to include (1) a classification schema of the levels of harm (e.g., mild, moderate, and severe) caused by procedures, housing conditions, or other adverse conditions affecting animal subjects; (2) a statement of how specific limits are to be determined by investigators and review committees (e.g., by behavioral and physiological criteria); and (3) lists of prohibited procedures and conditions that often cause severe or long-lasting harm.

In studies with a demonstrably low likelihood of significant suffering for animal subjects, it is not necessary to specify what counts as an upper limit to harm. This exemption is justified when procedures can be expected not to be significantly painful or distressing, housing conditions are appropriate for the species, and other factors affecting the lives of animal subjects pose no significant likelihood of harm. In these situations it may be acceptable for ethics review committees to classify a study as minimally harmful and therefore exempt from the requirement to identify an operational upper limit to harm.

Policies establishing an upper limit to permissible harm have been uncommon in animal research, but the European Union and a few countries are exceptions.²³ The relevant EU directive states: "From an ethical standpoint, there should be an upper limit of pain, suffering and distress above which animals should not be subjected in scientific procedures. To that end, the performance of procedures that result in severe pain, suffering, or distress [that] is likely to be long-lasting and cannot be ameliorated, should be prohibited."²⁴ The principle of upper limits to harm should be applied to experimental procedures, as in the EU directive, and also to housing conditions, transportation, and other factors that affect animal subjects' experience. The determination of acceptable upper limits of pain, distress, and suffering is left to the judgment of

investigators or ethics review committees in many jurisdictions. In the absence of public policies and deliberative bodies that establish upper limits and meticulously examine and monitor protocols to ensure conformity with these limits, loose risk–benefit assessments and unacceptable levels of harm to animal subjects may occur.

Policies that implement the principle of upper limits to harm should include a statement of when exceptions are justified, that is, a statement of the conditions that constitute rare, extraordinary cases that override the demands of the principle.

To recap this section, the three principles of animal welfare aim to promote the welfare of laboratory animal subjects in independent ways. The principle of no unnecessary harm requires abstaining from the imposition of harm whenever possible and, if harming is required for morally justified scientific purposes, minimizing the harm. The principle of basic needs requires meeting animal subjects' basic needs unless scientific procedures that have been demonstrated to be morally justified require that specific needs not be met. Finally, the principle of upper limits to harm requires that severe suffering not be caused to animal subjects for an extended period of time and allows exceptions to this requirement (that is, cases in which the principle is overridden) only if critically important social and scientific purposes are demonstrated.

The Crucial Role of Ethics Review Committees

In most countries the dominant model of oversight responsibility in the ethical review of animal research protocols is a local or national review committee that focuses on proper care and humane treatment as well as estimations and balancing of expected social costs, risks, and benefits of the research. The research is permitted only if the protocol has been reviewed for ethical acceptability and approved by the responsible committee. Some committees enlarge

the standard body of duties by placing responsibilities on committee members for the ongoing review of animal care and use (after approval of a protocol), postapproval monitoring, inspection of facilities, and the like. In some countries and institutions, committee members and staff working with animals are required to undergo instructional programs of training in animal welfare and protocol review.²⁵

The moral charge assigned to these committees for review and approval gives them a profoundly important role in the protection of animal welfare. Making committees a venue for the discussion of critical matters in animal research ethics is a particularly important strategy. The quality of review is generally enhanced when committees have their members in conversation about substantive, and sometimes contentious, matters of ethics. However, review committees frequently receive extensive data and resources that facilitate *scientific* evaluations (“good science”) without receiving comparably detailed resources to facilitate *ethical* analysis, argument, and justification (“good ethics”). Review should not occur in this imbalanced manner. These committees are, in ideal circumstances, primarily ethics review committees, not principally scientific review committees, although scientific expertise and a command of pertinent scientific information are usually essential for proper ethics review.²⁶

When functioning properly, animal care and use committees engage in the interpretation and specification of applicable moral norms, laws, government regulations, and scientific society guidelines. Committees can formulate institutional guidelines for particular issues such as control of pain, suffering, and distress to achieve consistency with the present framework of six principles. To maintain their integrity, these committees must conduct reviews in a way that is impartial and free of conflicts of interest that thwart objectivity in the appraisal of protocols. Review should never rest with investigators or other parties having a direct interest in the approval or disapproval of protocols.²⁷

Review committees will, to some extent, need to invoke local or national standards in their deliberations, which is unobjectionable when their standards are consistent with the six universally applicable moral principles articulated in the present framework of principles.

Scientific Necessity as a Justification for Causing Harm

Ordinarily it is wrong to harm an individual, whether human or animal, in the absence of a sufficient reason for doing so. But nearly all laboratory animal research involves foreseeable harm to subjects, and much animal research also requires not providing for some basic need. For this reason, the two principles of no unnecessary harm and meeting basic needs are formulated with qualifying conditions that permit some harming, including not meeting basic needs, when doing so is necessary for and morally justified by the social and scientific goals of research involving animals. The principle of upper limits to harm permits exceptions in rare cases of extraordinarily urgent social need. These qualifying conditions and permitted exceptions provide justifying reasons for allowing harm to occur when the harm would otherwise not be permitted.

Language in these three principles (and elsewhere in this document) such as “necessary for and morally justified by scientific purposes” does not mean that scientific purposes *by themselves* justify particular harms to animals or failures to meet specific basic needs in the course of research. The scientific objectives must be both *scientifically* justified by scientific standards (such as appropriate methods) and *morally* justified by moral standards.

Traditionally the major general justification for the use of animals in research has been the scientific necessity of using animals to achieve desirable research results such as human medical benefits. However, confusion often arises over the meaning and

moral significance of the term “scientific necessity.” The existence of a scientific necessity for using animals is a *morally necessary* but not a *morally sufficient* condition of justified uses of animals. The fact that the use of animals is scientifically necessary to achieve a valuable scientific result does not by itself render the research morally justified, because conditions other than scientific necessity must be met—namely, the conditions required by all six principles of the present framework.

On *The Principles of Humane Experimental Technique*

This framework of six principles is consistent with, while extending beyond, the influential “Three Rs” presented in *The Principles of Humane Experimental Technique* published in 1959 by zoologist and psychologist William M. S. Russell and microbiologist Rex L. Burch.²⁸ As their title indicates, their primary goal was to establish the principles that determine what qualifies as a *humane* experimental technique.

Their framework comprises three principles (the Three Rs):

- (1) *Replace* sentient animals by substituting for them either nonanimal methods or less sentient species (the principle of replacement);
- (2) *Reduce* the total number of sentient animals to be used in research (the principle of reduction);
- (3) *Refine* research techniques to decrease the amount and severity of the pain and distress experienced by animals in experiments and to increase their well-being (the principle of refinement).

These principles were designed to reduce the number of animals used while increasing the quality of research design and leaving

scientific objectives uncompromised. Russell and Burch declared that the threat of inhumanity in research settings is reduced or removed when these principles are observed. Their work has served historically as an influential call to improve ethics in animal research settings.

These three principles eventually came to be regarded as a system of *alternatives* to conventional programs of animal experimentation. The term “Three Rs” thereby became virtually interchangeable with the term “alternatives”; and the term “principles,” as used by Russell and Burch, was largely abandoned.²⁹ However, these authors did not propose merely a program of alternatives. One of their major goals was to capture what constitutes humane conditions in experimental inquiries by improving conditions of animal welfare. The Three Rs are perhaps best interpreted today as rules for protecting animal welfare because each promotes harm reduction.

An important historical legacy of the Three-Rs model is that research institutions have increasingly accepted the proposition that research is not justified unless no alternatives to the use of animals are available, the minimum number of animals essential to the research is used, and pain, distress, and suffering are minimized. This model stands as an admirable pioneering contribution to animal research ethics, but it is less morally comprehensive than the principles articulated in the present framework. In particular, this model fails to acknowledge that depriving research animals of basic needs constitutes harming that must be avoided or minimized. It also sets no limit on the severity and duration of permissible harm to animal subjects, despite its refinement requirement. Further, it is silent regarding which scientific objectives are worth pursuing in light of their scientific and social importance, their likely costs or risks to human beings, and the expected harms to animal subjects. On the whole, the Three-Rs framework overlooks the need for the second and third of the three principles of social benefit in the present framework and for a comprehensive

set of principles of animal welfare. The Three-Rs approach thereby neglects most of the necessary conditions of justified research involving animals that are articulated in the present document.³⁰

The framework of principles presented in this document is intended, in part, to close several gaps left by the Three Rs. A central objective is a set of moral principles that can withstand ethical scrutiny while providing useful guidance to investigators involved in research, animal care and use committees, professional societies, government agencies, funders of research, and academics. The framework of six principles is responsive to growing public concerns about animal welfare, advances in the scientific study of animals, and the maturation of animal ethics as a scholarly discipline—three circumstances that call for reconsideration and reconstruction of animal research ethics.

Notes

1. Professional associations, government agencies, and institutions that conduct animal research have issued practical directives for the care and use of animals, often covering subjects such as protocol review, selection of suitable animals, supervision by veterinarians, postprocedure care of animals, euthanasia, and minimization of stress, distress, discomfort, pain, and suffering. These directives sometimes use the language of “principles,” but they are typically not formulated as general moral principles of the sort provided in the present framework. For examples of the diverse ways the term “principles” is commonly used in animal research guidelines, see the several perspectives discussed in Diana E. Pankevich, Theresa M. Wizemann, Anne-Marie Mazza, and Bruce M. Altevogt, rapporteurs for the Institute for Laboratory Animal Research, Division on Earth and Life Sciences, *International Animal Research Regulations: Impact on Neuroscience Research—Workshop Summary* (Washington, DC: National Academies Press, 2012), chap. 7, “Core Principles for the Care and Use of Animals in Research,” <https://www.nap.edu/catalog/13322/international-animal-research-regulations-impact-on-neuroscience-research-workshop-summary>, retrieved 23 October 2018. This project was supported by contracts between the U.S. National Academy of Sciences and

a number of international organizations. See also Canadian Council on Animal Care, “CCAC Guidelines on: Animal Use Protocol Review (1997),” sec. 1, “General Principles,” https://www.ccac.ca/Documents/Standards/Guidelines/Protocol_Review.pdf, retrieved 29 November 2017. For other examples of the many different ways in which the term “principles” is understood in the literature of research involving animals, see the final section in the present document on Russell and Burch’s *The Principles of Humane Experimental Technique*; American Psychological Association (APA), Committee on Animal Research and Ethics, *Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research* (<http://www.apa.org/science/leadership/care/guidelines.aspx>, retrieved 11 January 2017), which relies in part on the American Psychological Association’s *Ethical Principles of Psychologists and Code of Conduct* (2002, amended 1 June 2010); Jerrold Tannenbaum, “Ethics and Pain Research in Animals,” *ILAR Journal* 40 (1999): 97–110; Paulina Górska, “Principles in Laboratory Animal Research for Experimental Purposes,” *Medical Science Monitor* 6 (2000): 171–80; Council for the International Organizations of Medical Sciences (CIOMS) and the International Council for Laboratory Animal Science (ICLAS), in partnership, *International Guiding Principles for Biomedical Research Involving Animals* (December 2012), <http://www.cioms.ch/images/stories/CIOMS/IGP2012.pdf>, retrieved 20 December 2016. CIOMS is an international, nongovernmental, and non-profit organization established jointly by WHO and UNESCO in 1949 (and an associate partner of UNESCO). ICLAS is a nongovernmental organization established in 1956 at the initiative of UNESCO, CIOMS, and the International Union of Biological Sciences (IUBS). In contrast to the aforementioned works, the “NASA Principles for the Ethical Care and Use of Animals” presents general moral principles for animal research, but the principles are notably vague and asserted without defense. See NASA Policy Directive 8910.1B (effective dates: 28 May 2008–28 May 2018), Attachment A, <https://nodis3.gsfc.nasa.gov/displayDir.cfm?t=NPD&c=8910&s=1B>, retrieved 7 August 2017.

2. Two issues and proposals regarding the justification of using animals in research are not discussed in this section, and no position is taken on their merit. The first maintains that the development of knowledge necessary for improving human health and well-being requires animal studies. The second argues that the use of animals has historically been necessary for many instances of progress in basic science and applied medical science. These approaches are principally about the *general justification of the institution* (or practice) of research involving animals. The focus of the present

framework of principles, by contrast, is on the *justification of particular animal research studies and protocols*. As the discussion of principles of social benefit makes clear, this framework assumes that the harmful use of animals in research is justifiable only if it presents a significant promise of social benefit. Additional discussion of the justification for and evaluation of animal studies appears later in this document. For informative general perspectives on the justification for using animals in scientific research, see two articles in Jerald Silverman, Mark A. Suckow, and Sreekant Murthy, eds., *The IACUC Handbook*, 3rd ed. (Boca Raton, FL: CRC Press of Taylor and Francis, 2014): Larry Carbone, "Justification for the Use of Animals" (211–36); and Ed J. Gracely, "Justification of the Number of Animals to Be Used" (237–53).

For rather optimistic approaches to the justification of the institution of animal research, see Nuffield Council on Bioethics, *The Ethics of Research Involving Animals* (Nuffield Council, 28 Bedford Square, London WC1B 3JS, May 2005), chap. 3, <http://nuffieldbioethics.org/wp-content/uploads/The-ethics-of-research-involving-animals-full-report.pdf>, retrieved 18 October 2018; Jane A. Smith and Kenneth M. Boyd, eds., *Lives in the Balance: The Ethics of Using Animals in Biomedical Research: The Report of a Working Party of the Institute of Medical Ethics* (Oxford: Oxford University Press, 1991); Kimberly A. Phillips, Karen L. Bales, John P. Capitanio, et al., "Why Primate Models Matter," *American Journal of Primatology* 76 (2014): 801–27; Larry Carbone, "The Utility of Basic Animal Research," in "Animal Research Ethics: Evolving Views and Practices," *Hastings Center Report Special Report* 42 (6) (2012): S12–S15; Larry Carbone, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy* (New York: Oxford University Press, 2004); D. Eugene Redmond, Jr., "Using Monkeys to Understand and Cure Parkinson Disease," in "Animal Research Ethics: Evolving Views and Practices," *Hastings Center Report Special Report* 42 (2012): S7–S11; and Simon Festing and Robin Wilkinson (Officers at the Research Defence Society in London), "The Ethics of Animal Research: Talking Point on the Use of Animals in Scientific Research," *EMBO Reports* 8 (2007): 526–30. Despite the optimistic outlook of these approaches, they uniformly recognize the moral status of animals and its importance in limiting what can be done to animals in research.

For more skeptical approaches regarding the justification of the institution of animal research, see Hugh LaFollette and Niall Shanks, *Brute Science: Dilemmas of Animal Experimentation* (New York: Routledge, 1996); C. Ray Greek and Jean Swingle Greek, *Sacred Cows and Golden*

Geese: The Human Costs of Experiments on Animals (New York: Continuum, 2000); Pandora Pound, Shah Ebrahim, Peter Sandercock, et al., "Where Is the Evidence That Animal Research Benefits Humans?" *BMJ* 328 (2004): 514–17; Robert A. J. Matthews, "Medical Progress Depends on Animal Models—Doesn't It?" *Journal of the Royal Society of Medicine* 101 (2008): 95–98; Kathleen M. Conlee and Andrew Rowan, "The Case for Phasing Out Experiments on Primates," in "Animal Research Ethics: Evolving Views and Practices," *Hastings Center Report Special Report* 42 (2012): S31–S34; Hugh LaFollette, "Animal Experimentation in Biomedical Research," in Tom L. Beauchamp and R. G. Frey (eds.), *The Oxford Handbook of Animal Ethics* (New York: Oxford University Press, 2011), 796–825; Pandora Pound and Michael Bracken, "Is Animal Research Sufficiently Evidence Based to Be a Cornerstone of Biomedical Research?" *BMJ* 348 (2014): g3387; Fiona Godlee, "How Predictive and Productive Is Animal Research?" *BMJ* 348 (2014): g3719; and Aysha Akhtar, "The Flaws and Human Harms of Animal Experimentation," *Cambridge Quarterly of Healthcare Ethics* 24 (2015): 407–19.

The present framework of principles assumes no position on the success or failure of these approaches to the justification of the institution of research involving animals. However, it is consistent with the recognition that these two general approaches are more compatible than they are commonly depicted in the literature on animal research ethics.

3. Several principles of the framework defended here are similar in content to the conditions of justified animal research identified in David DeGrazia and Jeff Sebo, "Necessary Conditions for Morally Responsible Animal Research," *Cambridge Quarterly of Healthcare Ethics* 24 (2015): 420–30.
4. Considerations other than requirements of the six principles sometimes come into play in animal research. One example involves a situation in which a particular group of animal subjects has been used in multiple demanding research projects because the animals are convenient for investigators to use, even though an alternative, less convenient group of animals is also available for use. Does multiple repeat use constitute unfairness or exploitation? Is it preferable to rank-order subjects so that individual animals recently involved in research are placed at the bottom of a priority list? Investigators or members of an animal care and use committee might judge that it would be unfair to continue using the same subjects over and over—a justice-based judgment not covered by the present framework of six principles.

5. Compare the similar conclusions reached by the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, Institute of Medicine (now Academy of Medicine), *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, DC: National Academies Press, 2011), <https://www.nap.edu/catalog/13257/chimpanzees-in-biomedical-and-behavioral-research-assessing-the-necessity>, retrieved 16 August 2017; National Institutes of Health, Office of the Director, "Statement by NIH Director Dr. Francis Collins on the Institute of Medicine Report Addressing the Scientific Need for the Use of Chimpanzees in Research," Thursday, 15 December 2011, <http://www.nih.gov/news/health/dec2011/od-15.htm>, retrieved 15 December 2011; and the follow-up report, Council of Councils, National Institutes of Health, *Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research: Report*, 2013, https://dpcpsi.nih.gov/council/pdf/FNL_Report_WG_Chimpanzees.pdf, retrieved 16 August 2017; National Institutes of Health, Announcement of Agency Decision: Recommendations on the Use of Chimpanzees in NIH-Supported Research, dpcpsi.nih.gov/council/pdf/NIHresponse_to_Council_of_Councils_recommendations_62513.pdf, retrieved 28 July 2013. See further Tom L. Beauchamp, Hope Ferdowsian, and John Gluck, "Where Are We in the Justification of Research Involving Chimpanzees?" *Kennedy Institute of Ethics Journal* 22 (September 2012): 211–42.
6. See Joseph Garner, "The Significance of Meaning: Why Do Over 90% of Behavioral Neuroscience Results Fail to Translate to Humans, and What Can We Do to Fix It?" *ILAR Journal* 55 (2014): 438–56; Ian Roberts, Irene Kwan, Phillip Evans, and Steven Haig, "Does Animal Experimentation Inform Human Healthcare? Observations from a Systematic Review of International Animal Experiments on Fluid Resuscitation," *BMJ* 324 (2002): 474–76; Carbone, "The Utility of Basic Animal Research," S12–S15; C. G. Begley, "Six Red Flags for Suspect Work," *Nature* 497, no. 7450 (23 May 2013): 433–34; Carol Kilkenny, Nick Parsons, Ed Kadyszewski, et al., "Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals," *PLOS ONE* (30 November 2009), <https://doi.org/10.1371/journal.pone.0007824>, retrieved 13 November 2018; Pound et al., "Where Is the Evidence That Animal Research Benefits Humans?" 514–17; Pablo Perel et al., "Comparison of Treatment Effects Between Animal Experiments and Clinical Trials: Systematic Review," *BMJ* 334 (2007): 197–200; LaFollette, "Animal Experimentation in Biomedical Research," 796–825; Kathleen R. Zahs and Karen H. Ashe,

“‘Too Much Good News’: Are Alzheimer Mouse Models Trying to Tell Us How to Prevent, Not Cure, Alzheimer’s Disease?” *Trends in Neuroscience* 33 (2010): 381–89; Andrew Rowan, “Debating the Value of Animal Research,” in Jeremy Garrett (ed.), *The Ethics of Animal Research* (Cambridge, MA: MIT Press, 2012): 197–214; Godlee, “How Predictive and Productive Is Animal Research?”; Akhtar, “The Flaws and Human Harms of Animal Experimentation”; Joseph Garner, Brianna N. Gaskill, Elin M. Weber, et al., “Introducing Therioepistemology: The Study of How Knowledge Is Gained from Animal Research,” *Lab Animal* 46, no. 4 (2017): 103–13; and Ulrich Dirnagl, “Is Translational Stroke Research Broken, and if So, How Can We Fix It?” *Stroke* 47 (August 2016): 2148–53.

7. The term “sentience” refers to the capacity for a particular type of conscious—that is, subjective—experience. Specifically, sentience is the capacity for sensations, feelings, or other experiences that are pleasant or unpleasant, agreeable or disagreeable, or attractive or aversive to the subject in virtue of how they feel. This type of experience plays a major role in moral thinking about animals. Because sentient animals have a subjective quality of life, they have an experiential welfare and therefore welfare interests. See note 14 for an explanation of the concept of interests.

Scientists cannot state with confidence precisely which species of animals are characterized by sentience and which are not. However, wide expert agreement exists on the basis of current scientific evidence that mammals and birds are sentient creatures. Arguably, the preponderance of evidence indicates that the range of sentient animals is considerably broader, including at least vertebrate species (possibly excepting jawless and cartilaginous fishes) and cephalopods (e.g., octopuses). It remains controversial whether some other animals commonly used in research—such as horseshoe crabs and fruit flies—are sentient, but available evidence does not refute this claim. For discussions of the empirical evidence and conceptual issues pertaining to the attribution of sentience, see David DeGrazia, “Sentience and Consciousness as Bases for Interests and Moral Status: Considering the Evidence,” in Syd Johnson, Andrew Fenton, and Adam Shriver (eds.), *Neuroethics and Nonhuman Animals* (New York: Springer, 2019); Colin Allen and Michael Trestman, “Animal Consciousness,” in Edward Zalta (ed.), *Stanford Encyclopedia of Philosophy*, substantive revision of 24 October 2016, esp. sections 6 and 7, <https://plato.stanford.edu/entries/consciousness-animal/>, retrieved 12 June 2017; Lynne Sneddon, “Evolution of Nociception in Vertebrates: Comparative Analysis of Lower Vertebrates,” *Brain Research*

Reviews 46 (2004): 123–30; David Edelman, Bernard Baars, and Anil Seth, “Identifying Hallmarks of Consciousness in Non-Mammalian Species,” *Consciousness and Cognition* 14 (2005): 169–87; Craig Mosley, “Pain and Nociception in Reptiles,” *Veterinary Clinics of North America* 14 (2011): 45–60; Krisopher Chandroo, Stephanie Yue, and Richard Moccia, “An Evaluation of Current Perspectives on Consciousness and Pain in Fishes,” *Fish and Fisheries* 5 (2004): 281–95; Colin Allen, “Fish Cognition and Consciousness,” *Journal of Agricultural and Environmental Ethics* 26 (2013): 25–39; Robert Elwood, “Pain and Suffering in Invertebrates?” *ILAR Journal* 52 (2011): 175–84; and Philip Low, drafter and ed., Jaak Panksepp, Diana Reiss, David Edelman, Bruno Van Swinderen, and Christof Koch, eds., “The Cambridge Declaration on Consciousness,” proclaimed in Cambridge, UK, 7 July 2012, at the Francis Crick Memorial Conference on Consciousness in Human and Non-Human Animals, at Churchill College, University of Cambridge, <http://fcmconference.org/img/CambridgeDeclarationOnConsciousness.pdf>, retrieved 12 June 2017.

For recent discussions asserting that some invertebrates other than cephalopods, such as certain insects and crustaceans, are likely sentient, see Andrew Barron and Colin Klein, “What Insects Can Tell Us about the Origins of Consciousness,” *Proceedings of the National Academy of Sciences* 113 (2016): 4900–4908; and Michael Tye, *Tense Bees and Shell-Shocked Crabs: Are Animals Conscious?* (New York: Oxford University Press, 2017). Related issues are treated in Kristin Andrews and Jacob Beck, eds., *The Routledge Handbook of Philosophy of Animal Minds* (New York: Routledge, 2018); and Michael Mendl and Elizabeth S. Paul, “Consciousness, Emotion and Animal Welfare: Insights from Cognitive Science,” *Animal Welfare* 13 (2004): 17–25.

The thesis that (at least most) vertebrates and cephalopods are sentient is broadly consonant with prominent systems of public policy governing uses of animals. For example, the U.S. *Public Health Service Policy on Humane Care and Use of Laboratory Animals* considers all and only vertebrate animals as falling within its protection (Washington, DC: National Academies Press, 1985; as revised 2015), Office of Laboratory Animal Welfare (OLAW), <http://grants.nih.gov/grants/olaw/references/phspolicylabanimals.pdf> (and also <https://grants.nih.gov/grants/olaw/references/phspol.htm>), retrieved 21 December 2016, 8. The European directive on animal research attributes sentience to vertebrates and cephalopods but not to other species. See the European Parliament and the Council of the European Union, Directive 2010/63/EU on the Protection

of Animals Used for Scientific Purposes, *Official Journal of the European Union* L 276/33, adopted September 2010, <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0063>, retrieved 19 October 2018.

8. It is disputed whether *insentient* animals have some level of moral status. This issue is outside the scope of the present framework of principles.
9. On what it means to say that an individual counts “in its own right,” see Allen Buchanan, “Moral Status and Human Enhancement,” *Philosophy & Public Affairs* 37 (2009): 346–81, esp. 346; and Frances M. Kamm, “Moral Status,” in *Intricate Ethics: Rights, Responsibilities, and Permissible Harm* (New York: Oxford University Press, 2006), 227–30.
10. A concise explication of the notion of moral status is the following: A particular individual X has moral status if and only if (1) moral agents have obligations regarding the treatment of X, (2) X has interests, and (3) the obligations are based on X’s interests; see David DeGrazia, “Moral Status as a Matter of Degree?” *Southern Journal of Philosophy* 46 (2008): 181–98, at 183. For the relevant meaning of “interests,” see note 14.
11. For discussions of such arguments in support of the thesis that animals have moral status, see Mary Anne Warren, *Moral Status: Obligations to Persons and Other Living Things* (Oxford: Clarendon, 1997); and Agnieszka Jaworska and Julie Tannenbaum, in Edward Zalta (ed.), “The Grounds of Moral Status,” *Stanford Encyclopedia of Philosophy* 2013, <http://plato.stanford.edu/archives/sum2013/entries/grounds-moral-status/>, retrieved 7 July 2017.
12. Some utilitarian theories, for example, hold that the prospect of net benefit justifies the harming of animal subjects whenever the prospect of benefit exceeds anticipated costs and harms, and no other option offers a superior balance of expected benefit over costs and harms. See, e.g., L. W. Sumner, “Animal Welfare and Animal Rights,” *Journal of Medicine and Philosophy* 13 (1988): 159–75. For the several roles utilitarian arguments play in assessing uses of animals in research (both in favor of and in opposition to various uses), see Robert Bass, “Lives in the Balance: Utilitarianism and Animal Research,” in Garrett (ed.), *The Ethics of Animal Research*, 81–105. Other theories, in contrast to utilitarianism, hold that maximizing expected net benefit, while necessary, is not sufficient to justify harming animals in nontherapeutic research. From this perspective, such use of animals must promise a substantial—as opposed to marginal—gain in utility (expected net benefit) when compared with the best alternative that does not use animals. See, e.g., Anne Barnhill, Steven Joffe, and Franklin Miller, “The Ethics of Infection Challenges in Primates,” *Hastings Center Report*

46 (2016): 20–26. Their discussion is limited to the use of nonhuman primates in infection challenge studies.

13. Although legal jurisdictions rarely accord rights to animals, some form of protective animal welfare laws exist in many countries in which animal research is conducted. Laws often treat animals as the property of owners, but scientific information about the mental complexity and needs of animals has increasingly steered animal research literature to proposals for the reform of laws and regulations.

The history of animal welfare law in Great Britain begins earlier than it does in other English-language countries. Two precedent-setting pieces of legislation in British law are (1) the Cruelty to Animals Act of 1876, which presents standard conditions that are legally obligatory when animals are used in research and creates a licensing system for animal experimentation (an act that amended the Cruelty to Animals Act of 1849); and (2) the Animals (Scientific Procedures) Act of 1986, which contains provisions governing the required use of general and local anesthesia and presents limits on the amount of pain, suffering, and distress to which an animal subject may be subjected. Since 1951, revised laws and regulations have been introduced and passed in the United Kingdom almost every decade. The British Animal Welfare Act 2006 is an act of Parliament that dates to the Protection of Animals Act of 1911, which it largely replaced. See further on the history of British law, Mike Radford, *Animal Welfare Law in Britain: Regulation and Responsibility* (Oxford: Oxford University Press, 2001).

By contrast, in the United States it was not until 1985, when Congress enacted the Improved Standards for Laboratory Animals Act, that a major stride was taken toward government-supported animal research guidelines (Public Law 99-198, Food Security Act of 1985, “Subtitle F-Animal Welfare”). This amendment to the Animal Welfare Act requires “a physical environment adequate to promote the psychological well-being of primates,” wording later incorporated into Animal Welfare Regulations, Title 9, Animals and Animal Products, Subchapter A (Animal Welfare), Parts 1–4 (9 CFR 1–4). The original Animal Welfare Act of 1966 (Public Law 89-544) in the United States was more symbolic than substantive until it was amended from 1985 through 2008. See also U.S. Interagency Research Committee, “U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,” in U.S. Department of Health and Human Services, National Institutes of Health, Office of Laboratory Animal Welfare (OLAW), as bundled

with *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, revision of 2015. In 2012 OLAW adopted the *Guide for the Care and Use of Laboratory Animals*, 8th edition released in 2011 by the National Academy of Sciences, Institute for Laboratory Animal Research (ILAR).

For a notably different North American document, see Canadian Council on Animal Care, *Guide to the Care and Use of Experimental Animals* (Ottawa: Canadian Council on Animal Care [CCAC]), vol. 1 (2nd ed. 1993), ed. Ernest D. Olfert, Brenda M. Cross, and A. Ann McWilliam, https://www.ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_Vol1.pdf, retrieved 19 October 2018 (vol. 2, 1984, is out of date and presumably under revision). The CCAC is a national peer-review organization that sets and oversees the implementation of standards for animal ethics and care in science throughout Canada.

See also Government of Australia (regulating studies funded by the National Health and Medical Research Council [NHMRC]), *Australian Code for the Care and Use of Animals for Scientific Purposes* (8th ed. 2013, <https://www.nhmrc.gov.au/guidelines-publications/ea28>, retrieved 25 March 2017). This code presents an “ethical framework” whose principles obligate researchers and teachers in Australia who use animals for scientific purposes; if research involves the use of nonhuman primates, the *NHMRC Policy on the Care and Use of Non-Human Primates for Scientific Purposes* governs the use of these animals in teaching and research, see [https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=NHMRC+Policy+on+the+Care+and+Use+of+Non-Human+Primates+for+Scientific+Purposes&*](https://www.google.com/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=NHMRC+Policy+on+the+Care+and+Use+of+Non-Human+Primates+for+Scientific+Purposes&*>), retrieved 25 March 2017.

For aspects of the history of such documents, see Bernard Rollin, “The Regulation of Animal Research and the Emergence of Animal Ethics: A Conceptual History,” *Theoretical Medicine and Ethics* 27 (2006): 285–304.

14. The term *interest*, as used in this document, refers to that which is in an animal’s welfare interest—that is, what is to the animal’s benefit or advantage (e.g., being under the care of a veterinarian), whether or not the animal desires it. An interest is an aspect of, or contributor to, an animal’s welfare. Welfare interests stand in contrast to preference interests, which may not serve an animal’s welfare—for example, a preference for eating unhealthful amounts and types of food. In this document, only welfare interests are under consideration. A *basic need* is an especially important category of welfare interest. Basic needs have a vital place in animal ethics because of their centrality to animal welfare.

15. The term “harm” does not entail a wrongful injuring or form of maleficence in the present framework of six principles, although some writers in ethics use the term with an evaluative meaning of one party wronging another. But individuals can be harmed without being wronged. For example, individuals can be harmed through disease, natural disaster, bad luck, or acts of others to which the harmed person consented.

As ordinarily understood, a harm is a thwarting, defeating, or setting back of the interests of one party by the conduct of another party or by natural events, so that the affected party is rendered worse off than before the event occurred or worse off than he or she would have been in the absence of the event. Accordingly, an individual is harmed whenever an interest is set back by a causal condition, whatever the type of causal condition. For an influential discussion of the nature of harm, see Joel Feinberg, *Harm to Others*, vol. 1 of *The Moral Limits to the Criminal Law* (New York: Oxford University Press, 1984), 32–36, 51–55, 77–78. In recent philosophical and legal literature, conceptual analysis of “harm” sometimes departs from the ordinary-language and law-based conceptions presented by Feinberg. See Seanna Shiffrin, “Wrongful Life, Procreative Responsibility, and the Significance of Harm,” *Legal Theory* 5 (1999): 117–48; Alastair Norcross, “Harming in Context,” *Philosophical Studies* 123 (2005): 149–73; Matthew Hanser, “The Metaphysics of Harm,” *Philosophy and Phenomenological Research* 77: 421–50; Elizabeth Harman, “Harming as Causing Harm,” in Melinda Roberts and David Wasserman (eds.), *Harming Future Persons* (New York: Springer, 2009): 137–54; and Ben Bradley, “Doing Away with Harm,” *Philosophy and Phenomenological Research* 85 (2012): 390–412.

16. Unpleasant experiences do not always involve suffering—for example, when an animal experiences mild transient pain or distress—but *extreme* experiential harm does always involve suffering. Accordingly, the term “suffering” is the sole term used here in characterizing the upper limit of permissible harm.
17. Guidelines and policies in animal research ethics generally underscore the importance of preventing harm. For example, policies requiring clean, sterile housing conditions are designed to facilitate the prevention of unplanned disease conditions among laboratory animals. See Institute for Laboratory Animal Research (ILAR), *Guide for the Care and Use of Laboratory Animals*, 8th ed., and American Association for Laboratory Animal Science (AALAS), “Performance-Based Criteria as the Basis for Determining Laboratory Animal Housing Standards,” <https://www.aalas.org/about-aalas/position-papers/determining-laboratory->

animal-housing-standards#.WHPTMfkrJxA, retrieved 8 January 2017. AALAS states: “Designing animal facilities that provide the basic needs of shelter, food, water, and a degree of environmental stability has long been appreciated. It is recognized that science has an ethical responsibility to house animals according to their species-specific needs” (citing Thomas L. Wolfe, “Environmental Enrichment,” *ILAR Journal* 46, no. 2 [2005]: 80). See also Robert M. Bigsby and Robin Crisler-Roberts, “Animal Housing, Use Sites, and Transportation,” in Silverman, Suckow, and Murthy, eds., *The IACUC Handbook*, 3rd ed.; and Federation of Animal Science Societies, *Guide for the Care and Use of Agricultural Animals in Research and Teaching*, 3rd ed. (January 2010), https://www.aaalac.org/about/Ag_Guide_3rd_ed.pdf, retrieved 11 June 2017. The members of many species of animals should be maintained in either natural habitats or ethologically appropriate physical and social environments. Ethical responsibilities to prevent harm are also of scientific importance. Pain, distress, and suffering in animals can skew and even invalidate scientific data, due to physiological and psychological side effects.

18. An informative set of insights regarding the identification and assessment of costs and benefits as well as practical procedures for cost–benefit assessment in the use of animals in research is found in a government-initiated document in the United Kingdom Animal Procedures Committee, *Review of Cost-Benefit Assessment in the Use of Animals in Research*, Home Office, 24 June 2003, <https://www.gov.uk/government/publications/review-of-cost-benefit-assessment-in-the-use-of-animals-in-research>, retrieved 27 March 2017; also https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119027/cost-benefit-assessment.pdf, retrieved 13 June 2017. See also Kathy Laber, Christian E. Newcomer, Thierry Decelle, et al., “Recommendations for Addressing Harm-Benefit Analysis and Implementation in Ethical Evaluation: Report from the AALAS–FELASA Working Group on Harm-Benefit Analysis, Part 2,” *Laboratory Animals* 50 (2016): 21–42; and Herwig Grimm, Matthias Eggel, Anna Deplazes-Zemp, and Nikola Biller-Andorno, “The Road to Hell Is Paved with Good Intentions: Why Harm-Benefit Analysis and Its Emphasis on Practical Benefit Jeopardizes the Credibility of Research,” *Animals* 7, no. 9 (2017): 1–6.
19. On the moral importance of the notions of “freedom from,” “freedom of,” and “freedom to,” see the historically influential “Brambell Report” (commissioned by the UK government), *Report of the Technical Committee to Enquire into the Welfare of Animals Kept under Intensive Livestock Husbandry Systems*, Cmd. (Great Britain, Parliament, 1965),

- H.M. Stationery Office, 1–84. Partially under the influence of this report, in July 1979 the British government established the Farm Animal Welfare Council (FAWC, today the Universities Federation for Animal Welfare, or UFAW), at the Old School, Brewhouse Hill, Wheathampstead, Hertfordshire AL4 8AN, UK). This body formulated policy that became known as the “five freedoms.” Its documents draw connections between the concepts of “welfare,” “sense of well-being,” and the “five freedoms.”
20. “Euthanasia,” as understood here, means the rapid and (ideally) painless killing of animals *for their sakes* and not merely for the purpose of avoiding costs or inconvenience associated with keeping them alive. On moral problems and appropriate practices of euthanasia by veterinarians, see American Veterinary Medical Association, *AVMA Guidelines for the Euthanasia of Animals: 2013 Edition*, <https://www.avma.org/KB/Policies/Documents/euthanasia.pdf>, retrieved 10 July 2016; Penny Hawkins, Mark J. Prescott, Larry Carbone, Ngaire Dennison, Craig Johnson, I. Joanna Makowska, Nicole Marquardt, Gareth Readman, Daniel M. Weary, and Huw D. R. Golledge, “A Good Death? Report of the Second Newcastle Meeting on Laboratory Animal Euthanasia,” *Animals* 6 (2016), https://www.researchgate.net/publication/306395197_A_Good_Death_Report_of_the_Second_Newcastle_Meeting_on_Laboratory_Animal_Euthanasia, retrieved 8 January 2017); and Canadian Council on Animal Care, *CCAC Guidelines on: Euthanasia of Animals Used in Science* (2010), <http://www.ccac.ca/Documents/Standards/Guidelines/Euthanasia.pdf>, retrieved 29 November 2017.
 21. See note 7 for references to literature on the state of scientific evidence and to relevant regulations.
 22. See Committee on Well-Being of Nonhuman Primates, Institute for Laboratory Animal Research (ILAR), Commission on Life Sciences, National Research Council, *The Psychological Well-Being of Nonhuman Primates* (Washington, DC: National Academies Press, 1998), www.nap.edu/openbook.php?record_id=4909&page=R1, retrieved 19 October 2018; United States Department of Agriculture (USDA) federal regulations, which provide “for a physical environment adequate to promote the psychological well-being of primates” (United States Code of Federal Regulations, 7 CFR 54, § 2143, 2.a.B, <http://int.search.myway.com/search/GGmain.jhtml?p2=%5ECAM%5Exdm101%5ES17547%5Egb&ptb=4832600C-DC52-4D23-AAA7-05B4FDA5ACBD&n=782b460f&ind=&trp=hpsb&trs=wtt&cn=gb&ln=en&si=32250788884&brwsid=def82325-cf72-46f8-b34e-5c9d5c26a4f5&searchfor=United%20States%20Code%20of%20Federal%20Regulations%2C%20Title%207%2C%20>

Chapter%2054%20%C2%A7%202143&st=tab, retrieved 24 December 2016); United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Animal Care, "Final Report on Environment Enhancement to Promote the Psychological Well-Being of Nonhuman Primates" (Riverdale, MD, 15 July 1999), part II, "Promoting Psychological Well-Being," https://www.nal.usda.gov/sites/default/files/environmentalenrichmentnhp_0.pdf, retrieved 9 January 2017; and American Psychological Association (APA), "Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research," sec. 3, <https://www.apa.org/science/leadership/care/guidelines.aspx>, retrieved 19 October 2018. An argument supporting the criterion of psychological well-being as well as the nutritional and environmental needs of animals in research is found in Phillips, Bales, Capitanio, et al., "Why Primate Models Matter."

23. The European Parliament and the Council of the European Union, Directive 2010/63/EU. See also European Commission, Scientific Committee on Health Environmental and Emerging Risks (SCHEER), Final Opinion, "The Need for Non-human Primates in Biomedical Research, Production and Testing of Products and Devices (update 2017)," https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_004.pdf, retrieved 29 November 2017.

A Canadian set of guidelines supplies another example despite its somewhat different language. The Canadian Council on Animal Care, "CCAC Guidelines on: Animal Use Protocol Review," states, in sec. 7 ("Setting Endpoints"): "Procedures that involve sustained and/or inescapable severe pain or deprivation in conscious animals, i.e., Category E experiments, are considered *highly questionable or unacceptable, irrespective of the significance of anticipated results*" (emphasis added). The CCAC's *Guide to the Care and Use of Experimental Animals*, vol. 1 (2nd ed., 1993, app. 15) states: "An animal observed to be experiencing severe, unrelievable pain or discomfort should immediately be humanely killed, using a method providing initial rapid unconsciousness." On the regulation of pain, see Larry Carbone, "Pain in Laboratory Animals: The Ethical and Regulatory Imperatives," *PLOS ONE* 6 (2011), <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0021578>, retrieved 22 October 2018.

24. Directive 2010/63/EU, Preamble 23; see also Preamble 22 and Articles 15, 38, 55, and Annex VIII. Compare the critical, yet sympathetic appraisal of this directive in Tom L. Beauchamp and David B. Morton,

“The Upper Limits of Pain and Suffering in Animal Research: A Moral Assessment of the European Union’s Legislative Framework,” *Cambridge Quarterly of Healthcare Ethics* 24 (October 2015): 431–47. For a contrast between American and European approaches to important aspects of this issue, see Baruch Brody, “Defending Animal Research: An International Perspective,” in Garrett (ed.), *The Ethics of Animal Research*, 53–66, esp. 55–58. For difficult cases of animal research that might, or might not, be judged justifiable exceptions to the principle of upper limits, see the infection challenges treated in Barnhill, Joffe, and Miller, “The Ethics of Infection Challenges in Primates,” and the biodefense research treated in Rebecca L. Walker and Nancy M. P. King, “Biodefense Research and the U.S. Regulatory Structure: Whither Nonhuman Primate Moral Standing?” *Kennedy Institute of Ethics Journal* 21 (2011): 277–310. Both compare the U.S. situation with developments in the European Union.

25. See, for example, the requirement that committee members and staff be familiar with an appropriate curriculum of professional moral discourse regarding the ethics of animal research in Max Planck Society, White Paper (2016), “Animal Research in the Max Planck Society,” Executive Summary, 36–37, <https://www.mpg.de/10972973/white-paper>, retrieved 8 May 2017. On the roles of continuing review and monitoring ongoing research, see two articles in Silverman, Suckow, and Murthy, eds., *The IACUC Handbook*, 3rd ed.: Gwenn S. F. Oki and Ernest D. Prentice, “Continuing Review of Protocols” (199–210) and Ron E. Banks, “Postapproval Monitoring” (719–50). The U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (as revised 6 June 2017) presents a lengthy list of “requirements” for proper training of members of Institutional Animal Care and Use Committees (IACUCs) and for compliance with Public Health Service (PHS) Policy. It states: “The U.S. Government Principles, Health Research Extension Act of 1985 and the PHS Policy repeatedly refer to appropriately trained, qualified, and experienced personnel, and availability of instruction and training. The institution is responsible for the training of its staff.” The PHS Policy requires training in humane experimental procedures, minimizing the number of animals required to obtain valid results, minimizing animal distress, potential dangers to and appropriate safeguards for animals, and the like. See “Frequently Asked Questions,” part G (“Institutional Responsibilities”), Question 1 (answer), <https://grants.nih.gov/grants/olaw/faqs.htm#G>, retrieved 13 June 2017.

26. This generalization needs further explanation such as that found in the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (as revised 6 June 2017): “The primary focus of the SRG (Scientific Review Group [at the National Institutes of Health]) is scientific merit and the primary focus of the IACUC [Institutional Animal Care and Use Committee] is animal welfare. The two bodies have different constitutions, mandates, and functions. However, since it is not entirely possible to separate scientific value from animal welfare, some overlap is inevitable. SRGs may raise concerns about animal welfare and IACUCs may question the scientific rationale or necessity for a procedure.” See “Frequently Asked Questions,” part D (“Protocol Review”), Question 12 (answer), <https://grants.nih.gov/grants/olaw/faqs.htm#628>, retrieved 13 June 2017. Research facilities in the United States appoint IACUCs to provide oversight of animal care and use programs and to function in accordance with the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals. See National Institutes of Health, OLAW, “The Institutional Animal Care and Use Committee,” <https://grants.nih.gov/grants/olaw/tutorial/iacuc.htm>, retrieved 25 December 2017. In many other countries the acronym is AEC (Animal Ethics Committee) or a functional equivalent, but the goals of the committees are comparable.

However, *policies* (or policy ideals) do not always capture committee *practices* in institutions of research. In the United States, the IACUC’s role is commonly taken not to be merely, or even primarily, that of an ethics committee in the usual sense. It therefore may be misleading to think of the work of these committees, as actually conducted, as even *principally* a matter of evaluating the ethics of research protocols. Their job is commonly regarded as the evaluation of protocols for both ethical merit (animal welfare protection and social benefit) *and* scientific merit (an evaluation that can incorporate a diverse set of criteria, including validity, or soundness, likelihood of yielding good data, promise of social benefit, and the like). Empirical research on committee practices suggests that there is no single standard approach, that committee members themselves often have strikingly different understandings of their roles, and that low rates of consensus frequently occur during protocol reviews. Minutes of IACUC meetings are often truncated, leaving little information about their work. Evaluation of the work of IACUCs is improved when minutes are sufficiently detailed to enable informed review by persons who were not in attendance or who are outside the membership of the committee—for

example, social scientists studying *how* these committees function and *how well* they function.

On these several problems regarding the functioning of IACUCs, see Applied Research Ethics National Association and Office of Laboratory Animal Welfare (ARENA and OLAW), *Institutional Animal Care and Use Committee Guidebook*, 2nd ed., 2002, secs. A–E, <https://grants.nih.gov/grants/olaw/guidebook.pdf>, retrieved 22 November 2017; Scott Plous and Harold Herzog, “Reliability of Protocol Reviews for Animal Research,” *Science* 293 (2001): 608–609, <http://www.socialpsychology.org/pdf/science2001-07-27.pdf?logged=true>, retrieved 22 November 2017; Silverman, Suckow, and Murthy, eds., *IACUC Handbook*, 3rd ed.; Gary Borkowski, Allison Hunter, Karl Field, and William M. Sischo, “Institutional Animal Care and Use Committees: A Survey Covering 10 Years of Experience,” *Journal of the American Association for Laboratory Animal Science* 36 (1997): 42–45, <http://www.ingentaconnect.com/content/aalas/jaalas/1997/00000036/00000005/art00002>, retrieved 22 November 2017; Catherine A. Schuppli, “Decisions About the Use of Animals in Research: Ethical Reflection by Animal Ethics Committee Members,” *Anthrozoös* 24 (2011): 409–25 (a study of practices in Western Canada); and Karen Graham, “A Study of Three IACUCs and Their Views of Scientific Merit and Alternatives,” *Journal of Applied Animal Welfare Science* 5 (2002): 75–81, <http://www.animalsandsociety.org/wp-content/uploads/2015/10/75-81-A-Study-of-Three-IACUCs-and-Their-Views-of-Scientific-Merit-and-Alternatives.pdf>, retrieved 22 November 2017.

27. See Canadian Council on Animal Care, “CCAC Guidelines on: Animal Use Protocol Review”; ARENA and OLAW, *Institutional Animal Care and Use Committee Guidebook*, 2nd ed.; and U.S. Code of Federal Regulations, Title 9, “Animals and Animal Products,” Ch. 1, §2.31 (9 CFR §2.31), Institutional Animal Care and Use Committee (IACUC), <https://www.gpo.gov/fdsys/pkg/CFR-2000-title9-vol1/pdf/CFR-2000-title9-vol1.pdf>, retrieved 25 March 2017; Rebecca Dresser, “Assessing Harm and Justification in Animal Research: Federal Policy Opens the Laboratory Door,” *Rutgers Law Review* 40 (1988): 723–95; Dresser, “Review Standards for Animal Research: A Closer Look,” *ILAR News* 32, no. 4 (1990): 2–7; Maggy Jennings and Sheila Silcock, “Benefits, Necessity and Justification in Animal Research,” *ATLA: Alternatives to Laboratory Animals* 23 (1995): 828–36; and O. Varga, P. Sandøe, and I. A. S. Olsson, “Assessing the Animal Ethics Review Process,” in Thomas Potthast and Simon Meisch (eds.), *Climate Change and Sustainable Development: Ethical Perspectives*

- on *Land Use and Food Production* (Wageningen: Wageningen Academic, 2012), sec. 17: “Animal Ethics,” 462–67.
28. William M. S. Russell and Rex L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959), commissioned by Universities Federation for Animal Welfare (UFAW); facsimile: Potters Bar, UK: Universities Federation for Animal Welfare, 1992. The history of the Three Rs and the idea of “alternatives” precede Russell and Burch’s work but have strong connections to their work. Major Charles Hume founded UFAW in 1926 to promote scientific knowledge, explicitly including scientific knowledge of ways to promote the welfare of animals. On the direct connections between Hume, UFAW, and the early work on alternatives—including Russell and Burch’s book—see Michael Balls, “UFAW and Major Charles Hume: The Wisdom of Russell and Burch,” *Pilas (Perspectives in Laboratory Animal Science)*, 27 February 2014, <http://pilas.org.uk/ufaw-and-major-charles-hume/>; and Balls, “The Principles of Humane Experimental Technique: Timeless Insights and Unheeded Warnings,” *Altex* 27, Special Issue (2010): 19–23. Balls refers to the Three Rs as “the Three Rs of UFAW” and regards Russell and Burch’s book as containing “timeless insights” into the proper use of laboratory animals. *The Principles of Humane Experimental Technique* is no longer in print, but the book is available at http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc (a website of Johns Hopkins University, Bloomberg School of Public Health), retrieved 22 October 2018.
 29. For works on the history, philosophy, and scientific methods of alternatives to animal research, see David Smyth, *Alternatives to Animal Experiments* (London: Scolar Press, 1978); Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *Animals and Alternatives in Testing: History, Science, and Ethics* (New York: Mary Ann Liebert, 1994); Ronald Hester and Roy Harrison (eds.), *Alternatives to Animal Testing* (Cambridge: Royal Society of Chemistry, 2006); Sarah Adler et al., “Alternative (Non-Animal) Methods for Cosmetics Testing: Current Status and Future Prospects—2010,” *Archives of Toxicology* 85 (2011): 367–485; R. D. Combes et al., “Early Microdose Drug Studies in Human Volunteers Can Minimize Animal Testing: Proceedings of a Workshop Organized by Volunteers in Research and Testing,” *European Journal of Pharmaceutical Sciences* 19 (2003): 1–11; Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, chap. 11; Andrew Rowan, “Ending the Use of Animals in Toxicity Testing and Risk Evaluation,” *Cambridge Quarterly of Healthcare Ethics* 24 (2015): 420–30; and the articles published in *ATLA: Alternatives to*

Laboratory Animals, a journal that lists the most recently published research papers on the subject of alternatives, <http://altweb.jhsph.edu/pubs/journals/atla/>, retrieved 26 December 2016.

30. For further discussion of the limitations of the Three Rs and the advantages of the framework presented in the present document, see David DeGrazia and Tom L. Beauchamp, "Beyond the Three Rs: Toward a More Comprehensive Framework of Principles for Animal Research Ethics," *ILAR Journal* (2019; published online first: doi: 10.1093/ilar/ilz011).

CRITICAL COMMENTARY BY
AUTHORITIES ON ANIMAL
RESEARCH ETHICS

The Potential and Impacts of Practical Application of Beauchamp and DeGrazia's Six Principles

Larry Carbone

I am honored to join Professors DeGrazia and Beauchamp in their efforts to clarify the ethical principles that should guide decisions regarding the use of animals in research. I come to this project as a laboratory animal veterinarian and historian of animal welfare policy. I focus in this commentary on the potential and impacts of practically engaging Beauchamp and DeGrazia's six principles, which they organize under the headings of "social benefit" and "animal welfare."

Laboratory animal veterinarians work in industry, government, and (my personal history) academic laboratories to oversee the health and welfare of research animals. Yes, though it seems odd at first, research programs employ teams of veterinarians to ensure that animals are healthy before they start on potentially quite harmful experiments, and that scientists respect limits on how much pain and suffering their animals will experience.

We veterinarians work closely with the Institutional Animal Care and Use Committees (IACUCs) that Beauchamp and DeGrazia describe. In my career, I was a founding member of the Cornell University IACUC when I was a veterinary student, and I now

direct the office that supports, staffs, carries out the staff training of, and executes the decisions of the IACUC at the University of California, San Francisco. In the field for more than thirty-five years, I've been the vet for thousands of laboratory animals and attended hundreds of IACUC meetings. I am a mouse and monkey doctor, with a long history of working under evolving laboratory animal welfare laws. My observations in this commentary are very much grounded in this hands-on clinical and regulatory work.

As a historian, an IACUC director, and primarily a veterinarian, I am interested here in how Beauchamp and DeGrazia's principles could lead to a wiser use of animals and better welfare outcomes in their lives. My contribution is to tie all of this experience as closely as possible to what we know about how IACUCs currently function and especially to what we know about animals' health, welfare, needs, and desires.

Expert Knowledge to Bring Principles into Practice

In 1996, David DeGrazia wrote, "The path to the ethical treatment of animals runs through their minds."¹ I join him in emphasizing the importance of understanding animals' mental lives—their sentience, intelligence, consciousness, self-consciousness, capacities for pleasure and pain—in judging the ethics of animal use.

Serious adherence to Beauchamp and DeGrazia's six principles could change some current practices and reinforce others. Moving forward with these principles requires better factual information about animals. Animal welfare scientists are working to better learn what animals need and what they want, and what brings them pleasure, pain, joy. For example, serious consideration of animal pain requires accurate knowledge of when and how much pain a mouse, monkey, or mollusk is experiencing, what treatments could be effective, and what effects the pain and the pain treatments can

have on data outcomes.² But this expert knowledge can reside with different experts, so we also need to consider policy shifts in who does what in terms of evaluating and scoring the animal welfare costs and the potential benefits a project carries.

All of this presupposes some facts and assumptions that already underlie our current practices and regulations, though they are not always explicitly stated: that sentient animals have interests we ought to consider; that sentience and moral status are on some sort of species continuum; that animal research does produce important, factually correct data that can benefit humans; that some human interests may be so important that they outweigh some serious animal interests; that causing or allowing pain, distress, and suffering requires justification proportionate to the degree of harm. Russell and Burch's Three-Rs framework organizes our thinking about improving animal welfare through the application of replacement, reduction, and refinement, but as DeGrazia and Beauchamp note, the Three-Rs framework does not address ethical questions of when we are justified in harming animals for the sake of research.

Currently, our practices are speciesist (humans outrank nonhumans, who themselves are not all equal) and centered on animals' experiential welfare. Current standards and regulations focus on animal pain, distress, and suffering as harms to animals, and they mostly consider painlessly killing healthy animals not to be morally problematic. We allow harms to animals, but not *carte blanche*: scientists' own sense of morality, various regulations, and their institutions' IACUCs set limits on what scientists may do with animals.³

As currently practiced in the United States, the six principles are already part of the research culture. Scientists must convince experts in their field of the social benefits of their projects and of the soundness and scientific merit of their experimental designs, their home institution IACUC that any harms are minimized but necessary, their veterinarian that their pain management plans are appropriate, and scientific journals that their findings are correct,

important, and worthy of publication. Despite this widely accepted culture of animal research ethics, I will here discuss ways in which a robust adoption of the Beauchamp and DeGrazia principles would substantially change current practices in balancing human benefits against animal harms and in conducting research in which pain medications will be intentionally withheld from the animals.

This discussion requires getting down into the biology and the administrative details of current practice.

Principle 3: The Principle of Sufficient Value to Justify Harm

DeGrazia and Beauchamp divide their six principles into the two broad categories of social benefit and animal welfare. Principle 3, the principle of sufficient value to justify harm, most explicitly raises the need to somehow quantify and balance the anticipated harms and risks of harm to animals against the potential benefits to people. Justification of this sort requires careful arguments to demonstrate that one is producing sufficient value (benefit) to justify any harm done. Quick assessments in the absence of such arguments would not satisfy the conditions of Principle 3.

Assessments of value (mostly to humans, many of them not yet born) and predictions of harm (mostly to animals) require detailed expert quantification and fact-finding. Experts on the research topic must evaluate and estimate the probability that a scientist's proposed project's design, methods, facilities, animal subjects, and personnel will produce new and usable knowledge about a particular disease or type of injury perhaps, or new knowledge in a basic science with no immediate known application to an identified health problem. Experts must establish and then evaluate the harms that animals are likely to experience, the likely success of mitigations and refinements, the numbers of animal subjects required to obtain statistically significant data, and the degree to

which pain mitigations as well as unmitigated pain may affect the animal data.

These data points—the probability of obtaining useful data that may affect future generations and the probability of variable harms to animals—are, of course, probabilistic and are proportional. We may rank projects' animal harms against each other and do the same for their likely benefits, but how do scales of low-to-high animal harm map onto scales of low-to-high data quality?

As Beauchamp and DeGrazia rightly point out, the evaluations do not end with the factual projections of data quality and degree of animal suffering. They also include the value of gaining the information from a given research program. And I again call attention to sorting out the facts required for ethical decision-making. In applied medical research, for instance, how prevalent is the disease? How serious is the condition in patients? Which preventions and treatments are already known?⁴ On the other hand, which resources will be required to manage the animals' health and housing?

Bateson proposed a schematic for a three-part evaluation of animal experiments, with one axis for the animals' suffering and two axes of benefit.⁵ I would combine "quality of research" and "certainty of benefit" into one axis, with "importance of the research question" as the third. DeGrazia and Beauchamp's principle requires asking three broad quantitative questions: How important is the research question being asked? How likely is the proposed research program to answer it? How much are animals likely to suffer in the course of the research?

A recent international working group⁶ has advanced an ambitious attempt to standardize what Bateson and others began, while cautioning, correctly I believe, that "there is no common 'currency' or value system for comparing the different realms of harm and benefit." For Principle 3, current practice entails a division of jurisdiction in which three separate bodies assess the importance of the research questions, the scientific merit of the proposed experiments, and the degree of animal harm, with partially overlapping expertise

and with no one of the three bodies accepting responsibility for doing what DeGrazia and Beauchamp call for, namely judging in a truly rigorous way how much prospective net benefit to society counts as sufficiently valuable to justify anticipated harms to the research subjects.

Thus there are at least three layers of evaluation—of the importance of the research, of scientific merit, and of harm to animal subjects—and too little connection between them. The first two relate to the limited financial resources available to a scientist planning an animal experiment. First, the pool of available funding is defined and limited in amount, whether by (1) Congress and government funding agencies deciding on levels of support for cancer versus mental health versus other disease areas; (2) the research money that foundations such as the American Heart Association raise and distribute; or (3) corporate priorities in pharmaceutical and biotechnology businesses. The expertise behind such allocation may include that of scientists as well as politicians, business executives, and the public's decisions on where to donate. Not every scientific proposal will receive a piece of these pies, and so groups of scientific (and other relevant experts) must convene both to peer-assess the projects most likely to produce important data or otherwise contribute to needed health outcomes and to recommend disbursement of the finite available funds. Financial limits in these two arenas sharply affect which animal experiments a scientist will be able to conduct.

In addition to the evaluations of the importance of the research and its scientific merit, there is IACUC review of potential animal harms. IACUC review may precede or follow scientific merit review, or they may occur simultaneously. A broad-based expertise in animal health and animal research methods may include no specialists in the scientist's own field of research. Among the IACUC's veterinarians, nonscientists, and scientists in other disciplines, for example, a brain cancer protocol might not be seen by either a cancer expert or a neurology expert. It's all in the makeup

of the particular IACUC. IACUCs are excellent at working to assess and minimize animal pain and distress, but even with a mandate in the American system to “weigh the objectives of the study against potential animal welfare concerns,”⁷ doing a true harm–benefit analysis goes beyond what many IACUCs are able to accomplish.

Crosstalk among these reviews is limited. An IACUC that reviews the animal welfare protocol prior to scientific merit review does so without knowing how much value true experts in the field will find in the work. The peer experts who review the scientific merit do not have access to the IACUC’s evaluations, even if the IACUC review is done first, and at most, grants officers will get an IACUC’s note of approval, not a quantitative score of the project’s animal welfare costs. Review bodies do not often see the three-dimensional cube that Bateson proposed. They do not see a quantitative welfare score lined up against a quantitative benefits score. How then to decide if there is sufficient benefit to justify harm?

A healthy adult human contemplating enrollment in a human clinical trial receives the scientist’s and the institutional review board’s evaluation of the values of the research and the possible projected harms if she volunteers. When adequately informed, she can weigh what it means *to her* to accept the risks and consent to participate. In many situations, she can withdraw consent at any point. Contrast this to animal research, where the animals have no voice and where even the most well-meaning discussions still revolve around how much animal harm the humans are comfortable imposing for a given set of experiments.

This fracturing of reviews is a question not just of who is reviewing, but also of what they are reviewing. Questions that straddle both the quality of the science and the welfare of the animals are the primary purview of one review body or another. Animal pain, for instance, is primarily the purview of the IACUC. Pain management would appear the quintessential issue for the welfare review by the IACUC and the in-house veterinarian, except that it is not. Without doubt, pain management is one of the most

important welfare considerations in many animal experiments. It should be simple for veterinarians and the IACUC to prescribe a pain management regimen for the animals used in a project, and if there were the slightest resistance from researchers, it would be over costs and scheduling of pain treatments. However, research scientists know very well that various painkillers can have profound effects throughout animals' bodies, and then on the data those bodies yield. Untreated pain similarly profoundly affects animals' biology, having a major impact on sleep patterns, food and water consumption, and immune function, and having other effects that go beyond welfare and affect how well the animal body yields high-quality data. Decisions about pain management—whether and how to treat pain—are simultaneously scientific questions of experimental design *and* questions of animal welfare, but currently are mostly just in the hands of the welfare body, the IACUC, which may not have the expertise to evaluate how pain management choices could lower the value and quality of the work. The IACUC also may lack the expertise to push back on scientists' concerns that for the sake of sound data they must under-treat animal pain. With current divisions of scientific and welfare review, and partitioning of what issues count as science versus welfare, meeting the principle of sufficient value to justify harm remains a challenge.

Principle 4: The Principle of No Unnecessary Harm

If animal research's only tools were binoculars for watching free-roaming animals or veterinary exams of farm and pet animals when they fall ill, the ethical issues would be few and the stakes low. But much of biomedical research includes inducing illnesses in animals, manipulating their genes, confining them in cages, or performing surgeries and other procedures aimed at making "models"

of the human biology and illness we are trying to study. Much of this work causes pain or distress to the animals.

Of the greatest concern are animal experiments with known high potential for pain, suffering, or distress, in which the scientist believes that measures to alleviate these conditions, especially the use of pain medications, would disrupt and invalidate the science. Beauchamp and DeGrazia's fourth principle, the principle of no unnecessary harm, covers this set of concerns, while Principle 6, goes further, calling for upper limits to harm. Necessary harm? Unnecessary harm? Unalleviated pain and distress? This discussion requires at least some detailed consideration of what animals actually experience as research subjects, which requires some graphic detail. But we cannot bring these principles into practice without looking at those facts in detail, somehow quantifying them and the alternatives, if we hope to increase the ethical score of our animal use.

Here is one of hundreds of examples. Glioblastoma is a devastating and common type of brain cancer or brain tumor. A scientist trying to develop new cures or better brain imaging diagnostics may choose to model this cancer in mice. She will not put out a call to veterinarians around the world to send her cases of mouse brain cancer that they diagnose; rather, she will *model* it by causing the disease in her laboratory mice. A common approach is to do a surgery, opening a small hole in the mouse's skull and injecting cancer cells. The cells are allowed to grow over several weeks, and once the brain tumor is established, the mouse is a "model" and the scientist can test some anti-cancer treatment, or study how to better diagnose this cancer, or study the mouse version of the normal course of the disease, such as which cell types infiltrate glioblastoma tumors or which activated genes the cancer cells contain.

My approach as a mouse veterinarian and IACUC member is to list the likely points of welfare concern during the life of such a mouse, and in this model, they are two. First, the surgery to create the model can cause pain and distress for some days until

the mouse recovers from the procedure. A few days after the surgical incision heals, the mouse is modeling early-stage human brain cancer, with a clinically silent tumor causing no headaches, seizures, or other symptoms. Only weeks to months later does the tumor reach a size where it starts to cause pain or neurological problems or other health issues for the mouse—this is the second point of welfare concern. The Three-Rs approach helps to guide our efforts to minimize these concerns, such as refining the surgical procedures to treat pain and, later, setting humane endpoints (such as early euthanasia of a still-asymptomatic mouse) if we can get all the data we need before the cancer becomes symptomatic. But the Three-Rs framework does not guide us on what to do when the refinements do not bring pain and distress to zero, that is, on what to do about the “necessary,” or at least unavoidable, harm to the animal subjects.⁸

Principle 4, the principle of no unnecessary harm, requires us to look closely at the model to see if there are any harms intentionally and knowingly inflicted (what Russell and Burch called *direct inhumanity*), as well as harms that are an unavoidable byproduct of research design (*contingent inhumanity*), and treat them with painkillers or by euthanasia so that animals’ suffering is kept to a minimum.⁹

DeGrazia and Beauchamp’s fourth principle does allow for harming research animals. This principle “requires efforts to reduce or eliminate the harm” but still allows harm when “the harm is unavoidable because of morally justified scientific objectives that satisfy the principles of social benefit.” Current regulations, like the fourth principle, likewise allow harm, but prohibit *unnecessary* harm and require justification of unalleviated pain and distress. Are Beauchamp and DeGrazia advocating something different?

Veterinarians and IACUCs excel at analyzing and reducing harms, but they face limits. In the glioblastoma example, it is possible (though the scientific literature on this is frustratingly sparse)

that drugs that could treat the mouse's surgical pain could interfere with the growth of the implanted tumor cells. Whatever postsurgical pain occurs would seem to meet current practice's and Beauchamp and DeGrazia's criteria of necessary harm. If this principle shifts current practice at all, it might be in requiring more robust analysis of the social benefit of the project. Otherwise, this is how IACUCs already work.¹⁰

No one in human patient care or in animal research should expect that pain medications will bring the postsurgical pain to zero; I am talking here about a situation where we knowingly plan to do less than the best for animal pain or distress. As a general principle, scientists have demonstrated differences in data outcomes when pain is treated versus untreated.¹¹ Sometimes, a scientist will theorize that pain medications *may* disrupt their data but without clear evidence for the specific studies he is planning; typically, the IACUC will accept this rationale and allow the untreated pain.¹² A major problem arises here: the scientific determination that pain management plans will make for data of poorer quality needs a robust examination. How strong is the effect? Is it specifically demonstrated for this model? How clear is it that, when data from treated animals and from animals in pain differ, it is the animals in pain that are somehow the truer or more accurate model? If pain medicines and untreated pain both affect immune function, for example, which immune effects are most disruptive to the quality of data an experiment may produce? This scientific evaluation of the effects of pain management is challenging enough, but Principle 3, the principle of sufficient value to justify harm, also requires a reckoning of whether any residual untreated pain is ethically justified in its balance of harms and benefits. It is one thing to consider the ethics of inflicting pain when we are also doing our best to minimize it. It is a special case to inflict animal pain and knowingly decide to undertake anything less than full treatment of that pain.

Principle 6: The Principle of Upper Limits to Harm

On first read, I thought Principle 6 was the most radical, at least in the United States. I've often said that in theory, at least, a U.S. IACUC can approve any animal procedure, so long as it believes that the harmful procedure is the only route to answering what experts in the field tell them is a desirable research question. Standards do differ in other countries or legal jurisdictions. For example, the European Union directive states, "There should be an upper limit of pain, suffering and distress," and procedures that lead to prolonged, severe suffering that cannot be ameliorated "should be prohibited."¹³

In truth, Principle 6, the principle of upper limits to harm, is not an absolute prohibition on animal suffering and therefore less of a departure from current practices than it seems at first glance. DeGrazia and Beauchamp allow that committees could approve exceptions in "rare, extraordinary circumstances." Current practice and law already require some setting of limits, but with a loose enough exemption clause that some 7 percent of American laboratory animals (of the minority of species covered by the Animal Welfare Act) are reported as suffering unalleviated pain or distress that is "more than slight or momentary."¹⁴ Beauchamp and DeGrazia set a higher threshold of what they would prohibit and a higher expectation of what it would take to allow an exception.

Current practice does indeed map onto this high threshold limit, for a small number of research procedures. The clearest example is the prohibition of paralytic drugs or neuromuscular blockers during painful procedures on unanesthetized animals. The fear is that such drugs render an animal helplessly paralyzed while undergoing such procedures, unable to escape, or even to clearly show by their behaviors that they are suffering. This in fact seems to be a long-standing and absolute prohibition in the Animal Welfare Act 2.31(d)(iv)(C) for the minority of species covered by that law.¹⁵

As I read this law, I find no room for an IACUC to allow an exception. Unspoken, though I believe just as strong, is the prohibition against any major surgery on unanesthetized animals, paralyzed or not, though with unparalyzed living animals, the technical challenges would make that close to impossible.

The precedent is long-established that some procedures are off the table. Serious embrace of Principle 6 would likely expand that suite of prohibited procedures, and I would start by adding surgery without any postsurgical analgesia, a practice that remains far too common. Scientists performing animal surgeries already need to factor in anesthesia as a potential complicating factor in their data. With a different upper limit on pain, scientists would need to factor in analgesic use in experimental and control animals as they do anesthesia, and work around the painkillers' effects on their data. Whereas Beauchamp and DeGrazia assign the IACUC and investigator the task of setting the upper limits and determining the rare exception, I would suggest clarity and detail at a national level, in national standards, as we have with the prohibition of paralyzing drugs.

Conclusion

Beauchamp and DeGrazia have articulated six related principles for the ethical use of animals in research. For the most part, these principles already exist, if not so clearly articulated, with varying impacts on practice. I believe the biggest departure from current practice would be some enhanced balance of animal harms to potential human benefits, whether in the hands of one body competent and expert in making both assessments or in a tighter coordination between a welfare-focused IACUC and an expert peer review scientific merit panel. Serious embrace of these principles would most likely shift common current harm-benefit evaluations further from animal harm, requiring a stronger than ever assessment

of social benefit in order to supply an adequate justification. Expert assessment of welfare, and of the potential benefits of proposed research, are integral, and the serious challenge is finding a way to rigorously make commensurate the incommensurate metrics of benefit and harm.

Acknowledgment

David Takacs provided very helpful suggestions on this commentary.

Notes

1. D. DeGrazia, *Taking Animals Seriously* (Cambridge: Cambridge University Press, 1996), 76.
2. B. Magee and R. W. Elwood, "Shock Avoidance by Discrimination Learning in the Shore Crab (*Carcinus maenas*) is Consistent with a Key Criterion for Pain," *Journal of Experimental Biology* 216 (2013): 353–58; L. U. Sneddon, "Pain in Aquatic Animals," *Journal of Experimental Biology* 218 (2015): 967–76; Larry Carbone, "Pain in Laboratory Animals: The Ethical and Regulatory imperatives," *PLOS ONE* 6 (2011), <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0021578>, retrieved 25 September 2018; L. U. Sneddon, et al., "Defining and Assessing Animal Pain," *Animal Behaviour* 97 (2014): 201–12; and Larry Carbone and Jamie Austin, "Pain and Laboratory Animals: Publication Practices for Better Data Reproducibility and Better Animal Welfare," *PLOS ONE* 11 (2016), <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155001>, retrieved 25 September 2018.
3. As DeGrazia and Beauchamp point out, current norms are ambivalent about death, or rather the killing of healthy animals, whether to obtain tissue for analysis or simply to cull unneeded animals at the end of an experiment. Informally, despite no regulatory requirement, many institutions do seek to place dogs, cats, monkeys, and some others in homes or sanctuaries when their research use has ended. And IACUCs will raise eyebrows at truly large numbers of mice or fish being killed in a

research program. Current rules, regulations, and practices are less ambivalent: under our rules, killing either is value-neutral or is morally required if it is done to limit pain and suffering. Only the method of killing comes under welfare review, to ensure that animals do not suffer pain and distress in the euthanasia process. A shift in our practices concerning painless killing of healthy animals would have enormous repercussions in laboratory animal care and use practices.

4. In biomedical research, some “basic science” projects are farther removed from imminent application to a known human health concern, but criteria for evaluating them are similar. In work that is closer to application, reviewers may look at the prevalence and severity of a particular infectious disease or cancer; in more basic research, justification is strongest when processes common to many cancers, or to immune responses to infection, are being examined. Given the complexity of our bodies and the myriad ways they can fail, virtually any new information about normal or abnormal bodily function is potentially valuable to human and veterinary medicine.
5. Patrick Bateson, “When to Experiment on Animals,” *New Scientist* 109, no. 1496 (20 February 1986): 30–32.
6. Institute for Laboratory Animal Research NRC, *Guide for the Care and Use of Laboratory Animals*, 8th ed. (Washington, DC: National Academies Press, 2011); K. Laber et al., “Recommendations for Addressing Harm-Benefit Analysis and Implementation in Ethical Evaluation,” *Report from the AALAS-FELASA Working Group on Harm-Benefit Analysis*, part 2, *Laboratory Animals* 50 (2016): 21–42; and A. Bronstad et al., “Current Concepts of Harm-Benefit Analysis of Animal Experiments,” *Report from the AALAS-FELASA Working Group on Harm-Benefit Analysis*, part 1, *Laboratory Animals* 50 (2016): 1–20.
7. Institute for Laboratory Animal Research NRC, *Guide for the Care and Use of Laboratory Animals*.
8. Cancer scares us for two opposite reasons: first, in its end stages it can be the most painful and debilitating of diseases; second, most cancers grow silently and painlessly, finally presenting only after months or years as palpable masses, painful lesions, or other symptoms. In animal-based cancer research, the majority of cancer studies are completed long before the animals get seriously symptomatic, and so as far as we know, most animals in cancer studies feel as healthy as animals without cancer.
9. W. M. S. Russell and R. L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).

10. Russell and Burch contrasted “direct inhumanity” to “contingent inhumanity.” In brain cancer studies, a researcher studying treatments for the pain of advanced cancers will induce “direct inhumanity,” intentionally allowing the painful condition so that she can study it. If she starts her project by surgically implanting cancer cells, any pain associated with the surgery is “indirect inhumanity,” a side effect of surgery that has no value for the experiment.
11. N. C. Peterson et al., “To Treat or Not to Treat: The Effects of Pain on Experimental Parameters,” *Comparative Medicine* 67 (2017): 469–82; Sneddon et al., “Defining and Assessing Animal Pain”; Carbone and Austin, “Pain and Laboratory Animals”; J. S. Mogil, “Animal Models of Pain: Progress and Challenges,” *Nature Reviews: Neuroscience* 10 (2009): 283–94; Russell and Burch, *Principles of Humane Experimental Technique*; S. Franchi et al., “Buprenorphine Ameliorates the Effect of Surgery on Hypothalamus-Pituitary-Adrenal Axis, Natural Killer Cell Activity and Metastatic Colonization in Rats in Comparison with Morphine or Fentanyl Treatment,” *Brain, Behavior, and Immunity* 21 (2007): 767–74; National Research Council (U.S.) Committee on Recognition and Alleviation of Pain in Laboratory Animals, *Recognition and Alleviation of Pain in Laboratory Animals* (Washington, DC: National Academies Press, 2009); and G. G. Page et al., “Evidence That Postoperative Pain Is a Mediator of the Tumor-Promoting Effects of Surgery in Rats,” *Pain* 90 (2001): 191–99.
12. Carbone and Austin, “Pain and Laboratory Animals: Publication Practices”; Larry Carbone, “Justification for the Use of Animals,” in J. Silverman et al. (eds.), *The IACUC Handbook*, 3rd ed. (Boca Raton, FL: CRC Press, 2014), 211–51.
13. European Commission (2010). Directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 and of the council of 22 September 2010 on the protection of animals used for scientific purposes. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:eN:PDF>
14. United States Department of Agriculture, *Animal Care Resource Guide*, Policy #11, Painful and Distressful Procedures, 2011, http://www.aphis.usda.gov/animal_welfare/downloads/policy/policy11.pdf, retrieved 10 October 2015.
15. United States Congress, “Subtitle F—Animal Welfare,” *United States Code Congressional and Administrative News*, 99th Congress, First Session, 1985 (St. Paul, MN: West, 1985), 2518–24.

Some Reflections on Primates in Research

Frans B. M. de Waal

The recommendations made by Beauchamp and DeGrazia in *Principles of Animal Research Ethics* make perfect sense to me, so my main objective here is to furnish refinements and extensions. My perspective reflects a lifelong career working with nonhuman primates at zoos and research institutions. I have worked in close interaction with biomedical researchers and neuroscientists and have myself conducted noninvasive studies of behavior and cognition. My main interest concerns the skills that allow primates to lead social lives, such as cooperation, conflict resolution, empathy, reciprocity, and power politics.

The code of ethics that we apply to other species is grounded in our estimation of their mental life, which in turn affects how much we respect them. In this regard we have gone through dramatic changes in the past couple of decades. Science has moved from the behaviorist view of animals as stimulus-response machines—the dominant view during most of the preceding century—to one in which animals are cognitive and emotional beings. Animal sentience has become a topic of serious debate,¹ and we now have countless studies of animal emotions,² empathy,³ and well-being.⁴ Part of this change in perspective comes from neuroscience. One cannot compare the role of the amygdala in both human phobias and the rat's fear response without assuming an evolutionary connection between the two.⁵ In the past twenty-five years, we also

have seen a sharp increase in studies of animal cognition, which has led to new insights about future planning, culture, theory of mind, cause-effect understanding, self-awareness, metacognition, and so on. We are used to a steady stream of new discoveries, which have blown big drafty holes in the wall that supposedly separates human cognition from that found in the rest of the natural world.⁶

Since continuity between us and other species is now more widely recognized than ever, our moral attitudes need to follow, a process that is well under way. When animals were still made out to be unfeeling automatons, we could do with them whatever we wanted. If animals are like rocks, we can throw them on a heap and stomp on them. If they are not, however, we have a serious moral dilemma on our hands with regard to the animals in our care, whether in the lab or in the agricultural industry with its much larger number of animals. It always boils down to how much gain justifies how much pain (presented by Beauchamp and DeGrazia as the principle of sufficient value to justify harm). This pain-to-gain balance is obviously affected by how much consciousness and sentience we are prepared to grant other species.

Indications are that all animals with brains, including arthropods and fish, modify their behavior following encounters with negative and positive stimuli.⁷ The capacity to learn is taken as evidence that these organisms must experience the impact of these stimuli in the form of pain or pleasure. The same evidence does not exist for animals without a central nervous system. But even if we assume that all animals with brains are sentient beings in that they have valenced experiences, this has not kept us from making finer distinctions about moral status. These distinctions appear rather arbitrary and are rarely grounded in any comprehensive theory, but we make them nonetheless. The differential value attached to animal lives may be based on their encephalization quotient, but also on our familiarity with them. Furry creatures generally fare better than scaly ones, and vertebrates better than invertebrates. We tend to place animals with large brains, such as elephants, apes, and

dolphins, above smaller-brained species, such as rodents, following a *Scala Naturae* conception of moral value, with our species at the apex. In this account, animals that are nearly as intelligent and socially complex as we are deserve the most consideration and highest moral status. This approach is illustrated by pleas for the legal rights of chimpanzees, the personhood basis for which often references similarities between apes and us.⁸ Due to its anthropocentrism, this is a tricky argument, because if the moral value of a species were to depend on how human-like it is, the inevitable implication would be that humans possess by far the highest moral value of all.

Given that I recognize sentience in all organisms with central nervous systems and given that sentience is about the only objective criterion we have for moral status, I am skeptical that we can move beyond this and assign differential status to animal lives based on brain size, longevity, similarity to us, or some other ostensibly objective criterion. Yet there is no denying that we do so all the time. I myself do so by placing higher value on the lives of apes than on those of most other species. Given that the majority of people have the same reactions, the Three Rs of research ethics (replacing, reducing, refining) are customarily extended with the “S” of a sliding scale. Accordingly, if an investigator requests the use of apes but could do the same work on monkeys, the apes are out. If an investigator proposes monkeys but could also work with rats, the monkeys are out. If an investigator proposes rats but could just as well work with fruit flies, the rats are out. This principle may not be easily justified, yet it is very much operative in practice. The “S” of the sliding scale explains, for example, why the National Institutes of Health (NIH) asked the Institute of Medicine (IOM) to explore how critical chimpanzees still are for biomedical research. It is not that the NIH wanted to stop all research on hepatitis, malaria, AIDS, or other diseases for which chimpanzees were being used, but simply wanted to determine if this one specific species, the chimpanzee, remained essential. The IOM committee reviewed and summarized the biomedical need for apes in a report released

in 2011, which summed up its conclusions as follows: “The present trajectory indicates a decreasing need for chimpanzee studies due to the emergence of non-chimpanzee models and technologies.”⁹

This report led to a ceasing of all NIH support for invasive biomedical studies on chimpanzees and a move of the remaining chimpanzees from laboratories to sanctuaries.¹⁰ That the NIH decided to retire chimpanzees, but not rats or any other typical laboratory species, is an illustration of the “S” factor in animal ethics. There were, of course, also external factors at work, such as public and political pressure, but it is no accident that greater pressure was exerted in relation to apes than any other laboratory species. We now see the same movement building for research on other primates, such as the rhesus macaques used in many labs.

On the gain side of the moral equation, the question is more complicated than perhaps suggested in *Principles of Animal Research Ethics*. The idea that the harmful use of animals in “research is justifiable only if it holds out a significant promise of social benefit” (p. 25) may be sound in theory, but it is difficult to implement in practice. On the one hand, there is the immediately useful biomedical research, such as when a new Ebola vaccine was tested on macaques before it helped avert a global pandemic in which millions of human lives might have been lost.¹¹ In this particular case, no one will argue with the need for animal research subjects. But there are also many studies concerning basic science the benefits of which for humanity are not immediately obvious, and perhaps not even their goal. Research on the effects of oxytocin, for example, started in the reproductive domain, in which this hormone plays a crucial role, but more recently has begun to explore its effects on bonding, social behavior, and empathy. Mostly conducted on rodents, these studies have yielded enough insight that the hormone is now being proposed as a treatment for autism spectrum disorder.¹² Science often follows such unintended paths, full of serendipity and chance discoveries, which may lead to genuine breakthroughs even if the initial research never hinted at such an application.¹³

The only aspects of animal research we can reliably judge are whether it is truly novel and whether the methodology is capable of providing the answers sought. In recent years, this question came up most prominently in relation to a study by Volkswagen Inc. on macaques at the Lovelace Respiratory Research Institute in Albuquerque, New Mexico, exposed to harmful exhaust gases, including nitrogen dioxide. It was unclear what answer they were after, except for one that the company could use to advertise its cars as “clean.”¹⁴ Volkswagen installed software in its cars to falsify the amount of emissions in the laboratory reports, which as a result were lower than those on the road, a crucial detail that also applied to the cars tested on monkeys. This detail was apparently unknown to the scientists involved, which made the procedure ethically problematic since (1) it failed to test what it was supposed to (namely, actual exhaust fumes of a running diesel engine), and (2) it was not designed to answer any fundamental science question to which we didn’t already know the answer (e.g., are toxic fumes bad for our health?). Clearly, no animals should ever have been used for a deliberately rigged experiment.

Apart from ethical considerations of what kinds of experiments to conduct on what kinds of animals, there is the issue of how animals should be housed. Since these are the conditions research animals face more than 90 percent of the time, this is a critical issue, but often neglected. The National Research Council’s *Guide for the Care and Use of Laboratory Animals* supports social housing as the default condition for primates and states explicitly, “Like all social animals, nonhuman primates should normally have social housing.”¹⁵ Yet at most research facilities that I know, the majority of primates still live in single cages or in pairs. The latter is obviously an improvement, but given that primates evolved for life in large multi-male multi-female groups, pair-housing is still inadequate. Primates thrive in a social setting. Whether they bicker or groom, they are made to live together.

A common argument by researchers against group housing is that certain procedures require daily access to the animals. This is a poor argument, however, given how easy it is to train primates to come out of their group. All you need to do is call them by name and open a door. In fact, many experiments could be done on a volunteer basis, provided they were enjoyable for the animals. At the Primate Research Institute in Inuyama, Japan, for example, the chimpanzees' outdoor enclosure has cubicles that the apes can enter any time to work by themselves on a computer screen. They can also leave any time they want. A video camera tells the investigators whose digital data they are looking at. We really don't need constant access anymore given the advances in wireless technology and microchips, which allow primates to be semi-free while being studied. At the Yerkes National Primate Research Center's field station, for example, rhesus macaques live in large outdoor corrals in groups of about one hundred. With a little creativity and technology, these conditions can accommodate almost any kind of research. Ideally, primate facilities would ditch all of their small cages and restraining chairs, and monitor the vital functions of their animals while they enjoyed the company of others. It would be better for the monkeys as well as produce better science. I know many places both in Europe and in the United States where scientists and information technology specialists are joining forces to achieve this goal.¹⁶ To force facilities in this direction, transparency will be key. Primate centers should open their doors to the press and public, allowing them to come take a look, either in reality or via live webcams.

To illustrate how important social life is, let me relate what happened one day when we gave our chimpanzees at the Yerkes Primate Center a brand-new climbing structure in their large enclosure. We had confined the whole colony for a few weeks in order to erect a huge wooden frame with ropes and nests high above the ground in their grassy outdoor area. When we released the colony, we expected that the apes would rush into the structure and enjoy the sights. They had been separated into various

indoor areas, however, and engaged in an emotional reunion instead. They barely glanced at the new construction, having only eyes for each other while hooting with excitement. They walked from one to the other, touching, kissing, and embracing their long-lost friends and family. The big moment was intensely social. Inspection of the new climbing frame could wait. Whenever we seek to provide optimal housing, we should remember that, even if physical conditions, space, and toys are important, the most enriching aspect of a primate's life is its social environment.

Ideally, research facilities would move toward a situation in which primates were in the company of familiar others *all the time*, even while being tested. This would represent a giant leap forward in terms of animal well-being, but it would also yield more ecologically relevant science because, after all, the goal is to serve the health and well-being of humans with social lives. This more enlightened approach, made possible by technical advances already in existence, would then be complemented by the more careful ethical justification of research proposed in this volume.

Notes

1. Kristin Andrews and Jacob Beck, *The Routledge Handbook of Philosophy of Animal Minds* (Oxford: Routledge, 2018).
2. Marc Bekoff, *The Emotional Lives of Animals: A Leading Scientist Explores Animal Joy, Sorrow, and Empathy—And Why They Matter* (Novato, CA: New World Library, 2007).
3. Frans B. M. de Waal, *The Age of Empathy: Nature's Lessons for a Kinder Society* (New York: Three Rivers Press, 2009).
4. Marian Stamp Dawkins, "From an Animal's Point of View: Motivation, Fitness, and Animal Welfare," *Behavioral and Brain Sciences* 13 (1990): 1–9; and Michael Mendl and Elizabeth S. Paul, "Consciousness, Emotion and Animal Welfare: Insights from Cognitive Science," *Animal Welfare* 13 (2004): 17–25.
5. Jaak Panksepp, *Affective Neuroscience: The Foundations of Human and Animal Emotions* (New York: Oxford University Press, 1998).

6. Frans B. M de Waal, *Are We Smart Enough to Know How Smart Animals Are?* (New York: Norton, 2016).
7. Victoria Braithwaite, *Do Fish Feel Pain?* (Oxford: Oxford University Press, 2010); and Barry Magee and Robert W. Elwood, "Shock Avoidance by Discrimination Learning in the Shore Crab (*Carcinus maenas*) is Consistent with a Key Criterion for Pain," *Journal of Experimental Biology* 216 (2013): 353–58.
8. Steven Wise, *Rattling the Cage: Toward Legal Rights for Animals* (New York: Perseus, 2000).
9. Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, Institute of Medicine (now Academy of Medicine), *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, DC: National Academies Press, 2011), 5.
10. Frans B. M. de Waal, "Research Chimpanzees May Get a Break," *PLOS Biology* 10 (2012), <http://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.1001291&type=printable>, retrieved 20 June 2018.
11. Thomas W. Geisbert, Kathleen M. Daddario-DiCaprio, Mark G. Lewis, et al., "Vesicular Stomatitis Virus-Based Ebola Vaccine Is Well-Tolerated and Protects Immunocompromised Nonhuman Primates," *PLOS Pathogens* 4 (2008), <http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1000225>, retrieved 19 June 2018.
12. Larry J. Young and Catherine E. Barrett, "Can Oxytocin Treat Autism?" *Science* 347 (2015): 825–26.
13. Morton A. Meyers, *Happy Accidents: Serendipity in Modern Medical Breakthroughs* (New York: Arcade, 2007).
14. Jani Actman and Rachel Bale, "Was Volkswagen the First to Test Exhaust Fumes on Monkeys? Your Questions Answered," *National Geographic*, 9 February 2018, <https://news.nationalgeographic.com/2018/02/wildlife-watch-lab-monkey-testing-volkswagen-auto-industry/>, retrieved 18 June 2018.
15. National Research Council of the National Academies, *Guide for the Care and Use of Laboratory Animals*, 8th ed. (Washington, DC: National Academies Press, 2011), 58.
16. Regina Paxton Gazes, Emily Kathryn Brown, Benjamin M. Basile, and Robert R. Hampton, "Automated Cognitive Testing of Monkeys in Social Groups Yields Results Comparable to Individual Laboratory-Based Testing," *Animal Cognition* 16 (2012): 445–58.

Putting the Ethical Principles into Practice

Rebecca Dresser

In “Principles of Animal Research Ethics,” Tom Beauchamp and David DeGrazia introduce a framework of core values and principles for studies involving nonhuman animals. Theirs is a more comprehensive approach than the leading alternative, Russell and Burch’s Three-Rs framework, which focuses on replacing, refining, and reducing laboratory animal use.¹

Beauchamp and DeGrazia see the Three-Rs framework as a significant step forward in recognizing the moral value of animal welfare, but they also see it as insufficient. Their own framework incorporates additional moral considerations relevant to animal research. It is to some extent modeled on the influential *Belmont Report*, which addresses the ethics of research involving human subjects.² Animal research needs an analogous ethical guide, and Beauchamp and DeGrazia have constructed one.

Although animal research and animal protection advocates hold opposing positions on many issues, Beauchamp and DeGrazia believe that advocates on both sides would (and should) agree with the following three claims:

- (1) sentient animals have moral status and therefore are not merely tools of research;
- (2) the only possible justification for (nontherapeutically) harming animals . . . is the prospect of substantial and otherwise unattainable social benefits; and

- (3) any permissible harming of animals in research is limited by considerations of animal welfare (p. 2).

Building on this idea of a values consensus, Beauchamp and DeGrazia propose six principles to guide the ethics and regulation of animal research. Three principles flesh out the social benefit requirement: (1) there must be no available and ethically acceptable alternative way to investigate the scientific question; (2) an animal study's potential social benefit must exceed the potential human harm and other costs that result from poor-quality or inapplicable animal data; and (3) a study's expected net benefit must be valuable enough to justify the expected harm to animals.

Beauchamp and DeGrazia's remaining principles elaborate on animal welfare values: (1) the study of harms to animals must be "necessary for and morally justified by" (pp. 12 and 18) the research objective; (2) researchers and institutions must ensure that laboratory animals' basic needs are met; and (3) study animals must not be subjected to extended, severe suffering except where this suffering is necessary for and justified by a study's "critically important social and scientific purposes" (p. 12).

The values underlying these principles may be widely shared, but that doesn't mean that they are widely observed. As Beauchamp and DeGrazia acknowledge, "[T]he implications of these values are not always adequately appreciated in policy and practice" (p. 3). Beauchamp and DeGrazia offer a conceptual roadmap for translating the values and principles into meaningful changes in the conduct of animal research, but substantial implementation challenges remain.

I believe that additional action will be needed to promote real moral progress in this area. In this commentary, I describe how the oversight system could and should be altered to promote on-the-ground application of the values and principles embodied in Beauchamp and DeGrazia's valuable contribution. I focus on two elements of research oversight: the research ethics review

committee and the study proposal review process. I recommend three changes that would make Beauchamp and DeGrazia's framework a real force in the conduct of animal research.

The Ethics Review Committee

As Beauchamp and DeGrazia note, countries generally rely on interdisciplinary ethics review committees to determine whether proposed animal studies should go forward. Given the availability of other regulatory models, why have countries chosen this one? What explains the popularity of committee oversight?

The institutional committee mechanism is attractive for several reasons. Not everyone accepts the consensus values Beauchamp and DeGrazia describe. Animal research remains a contentious issue in the United States and other countries invested in the scientific enterprise. On one end of the spectrum are militant animal rights groups contending that laboratory animals deserve the same protection as human research subjects. On the other end are research advocates who see animals primarily as research tools.

In this climate, decisions on animal research are controversial. Government officials reluctant to take sole responsibility for the decisions have diverted some of the responsibility to institutional ethics review committees. The existence of ethics review committees reassures the public that "someone" is paying close attention to how local research institutions treat the animals housed in their facilities. Institutional oversight also allows the government to avoid some of the costs and burdens imposed by regulatory systems that rely solely on government workers for enforcement.

Moreover, the committee mechanism fits with the traditional U.S. approach to research oversight. The committee approach was first adopted in the 1970s, when the government incorporated it into U.S. regulations for research involving human subjects. Officials prescribed broad substantive principles to guide human

studies, but required research institutions to assemble an interdisciplinary committee of scientists and clinicians, as well as community members and other nonscientists, to evaluate whether human research proposals were consistent with the principles.³

The committee mechanism also emerged as the favored method for addressing ethical dilemmas in treatment decision-making for seriously ill persons. Hospital ethics committees became the venue for considering difficult patient care cases. Institutional committee review has been incorporated into oversight systems governing research involving biohazards, radiation, and embryonic stem cells as well. So it's not surprising that officials see institutional ethics committees as the proper forum for evaluating animal research proposals.

But animal research review committees have their critics, too. As Beauchamp and DeGrazia point out, committees don't always engage in the sort of analysis and debate that is necessary for a full-throated ethics review. Those favoring greater protection for laboratory animals argue that committees are dominated by researchers and others committed to the scientific enterprise, rarely including members who are genuine advocates for animals.⁴ Critics also argue that committees allow individual members to feel less responsible for controversial choices than they would if they were assigned sole responsibility for such choices. Critics point to inconsistent decision-making by committees, too, for study methods deemed ethically unacceptable by one committee are sometimes permitted by another.⁵

Committee defenders and critics make valid points, for committee performance over the years reveals both strengths and weaknesses. In my view, committees have contributed to material progress in promoting the animal welfare values underlying Beauchamp and DeGrazia's principles, but have been less successful in applying the social benefit values they describe.

On the positive side, committees have played a significant role in promoting what Russell and Burch called "refinement," which

refers to a decrease in the incidence or severity of harm imposed on laboratory animals. Committees have helped investigators find ways to conduct their studies more humanely than they initially planned to do. Veterinarians and experienced animal researchers play a crucial role in suggesting alternative strategies that will impose less harm on animal subjects. Since committees were put into place, many techniques have been devised that allow laboratory animals to lead more comfortable lives. Social housing and enriched environments are more common than they once were.⁶

These committee accomplishments are morally significant, and I do not want to trivialize them. But committees rarely engage in meaningful review of the moral justification for the animal studies they consider. I believe that changes in the oversight system are needed to satisfy Beauchamp and DeGrazia's social benefit requirement for animal research.

Toward Rigorous Social Benefit Review

As Beauchamp and DeGrazia point out, animal research review committees "have a responsibility to evaluate whether [study] justifications offered by investigators are adequate" (p. 6). This means that "review committees must judge how much prospective net benefit to society counts as sufficiently valuable to justify anticipated harms to the research subjects" (p. 9). This is a formidable assignment, and U.S. government rules on animal research supply little guidance on how to fulfill it.

A rigorous inquiry into research justification would require committees to evaluate the significance of each study proposal's objectives. Animal research seeks information on a variety of human health problems, from life-threatening conditions to relatively minor ones. Studies are also aimed at advancing less compelling objectives, such as a company's financial interests or a

researcher's professional success. Which of these objectives are important enough to justify imposing harm on laboratory animals?

A rigorous justification assessment would also require committees to consider the likelihood that animal studies will generate information that is of good quality and relevant to humans. It would require in-depth evaluation of whether the human interests at stake could be satisfied by an alternative approach to knowledge-gathering. This is a serious challenge, for contrary to the conventional wisdom, animal research itself may not be the best way to learn about human health problems. The philosopher T. L. S. Sprigge once observed, "In all cases, some probability attaches to the hypothesis that if the certain pain and evil to animals were stopped, humanity would find another means to the same end, or would divert its resources to even better ends."⁷ The translational science movement has revealed many problems with the traditional reliance on animal models in biomedical research.⁸

In view of the literature addressing animal research review committees, as well as my own experience serving on several of them, I believe that committees generally demand little more than a perfunctory claim to research value to justify significant animal harm. I have seen committees disapprove student projects entailing extensive animal harm, on grounds that the projects' benefit both failed to outweigh the harm to animal subjects and could be achieved through alternative means. As a general rule, however, committees are reluctant to reject proposals on this basis. I would be shocked, for example, if a committee disapproved a proposed animal study addressing a minor health matter, such as athlete's foot, because a new remedy for the ailment is not all that important to society. I would be shocked as well if a committee turned down a proposed animal study because its findings would not be sufficiently relevant to human health.

In their current form, the vast majority of animal research review committees are unprepared and unequipped to perform a rigorous evaluation of study justifications. A commitment to Beauchamp

and DeGrazia's principles requires a more robust justification review than proposals now receive. Assessment of research justification will always be an imperfect process, but three policy changes could increase the chance that proposed animal studies will undergo more stringent justification review.

One positive change would be a requirement to increase the diversity of institutional committee membership. Animal research review committees should include more "outside" members than they currently do. They should include people holding a wide range of views on the morality of using animals in research, including individuals with a strong commitment to animal protection. As Beauchamp and DeGrazia observe, "[T]he quality of review is generally enhanced when committees have their members in conversation about substantive, and sometimes contentious, matters of ethics" (p. 19). Without a diverse group of people at the table, conversation like this is unlikely to occur.

The creation of a better scientific review system would also improve the justification assessment. If an animal study fails to meet high scientific standards, it will not produce worthwhile knowledge. The existing government provisions on animal research direct committees to consider scientific quality, but fail to provide committees with the tools to do so. Institutional committees lack the time and resources to establish a system in which proposals undergo in-depth evaluation of research quality.

Although some animal study proposals are subjected to relatively stringent peer review as part of the government funding process, others are not. Current policy provides no assurance that proposals seeking funding from nonprofit organizations, commercial sponsors, or research institutions will be subjected to rigorous scientific scrutiny. A comprehensive scientific review program would be a valuable addition to research oversight. If every animal study proposal had to be rigorously examined for scientific quality before coming to the ethics review committee, committees could do a better job of determining which studies should go forward.⁹

Setting limits on the number of animals that may be used in research is another policy change that would enhance justification assessment in the study review process. Guidance on developing such an approach comes from the U.S. National Institutes of Health's research funding review program. In the funding context, highly qualified experts consider how to allocate scarce monetary resources among competing projects. The limited resources available to support research are channeled to the most promising and important projects, while lower-quality proposals go unfunded.

Animal research policy should adopt a similar approach. Laboratory animals should be regarded as "scarce moral resources" to be reserved for the highest-quality studies. In such a system, officials would cap the number of laboratory animals that could be used during a given time period. Scientific reviewers and institutional committees would be assigned to rank proposals according to their importance. Such a system would compel decision-makers to engage in a more stringent justification evaluation than they currently perform.

There are significant financial and ideological impediments to securing the policy changes I recommend. But without changes like these, I fear that Beauchamp and DeGrazia's important conceptual work will have little real impact on the conduct of animal research. A commitment to their ethical framework demands a commitment to the concrete actions that could make it a reality.

Notes

1. William M. S. Russell and Rex H. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).
2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, DC: DHEW Publication OS 78-0012, 1978), <https://www.hhs.gov/ohrp/>

regulations-and-policy/belmont-report/read-the-belmont-report/index.html, retrieved 20 March 2018.

3. See Charles McCarthy, "The Origins and Policies That Govern Institutional Review Boards," in Ezekiel Emanuel et al. (eds.), *The Oxford Textbook of Clinical Research Ethics* (New York: Oxford University Press, 2008), 541–51.
4. See generally Andrew Rowan, "Ethical Review and the Animal Care and Use Committee," *Hastings Center Report* 20, no. 3 (1990): 19–24.
5. Scott Plous and Harold Herzog, "Reliability of Protocol Reviews for Animal Research," *Science* 293 (2001): 608–609; Rebecca Dresser, "Developing Standards in Animal Research Review," *Journal of the American Veterinary Medical Association* 194 (1989): 1184–91.
6. See generally Rebecca Dresser, "Assessing Harm and Justification in Animal Research: Federal Policy Opens the Laboratory Door," *Rutgers Law Review* 40 (1988): 723–95. For reports on efforts to promote enrichment, see David Grimm, "The Happiness Project," *Science* 359 (2018): 624–27; S. W. Dean, "Environmental Enrichment of Laboratory Animals Used in Regulatory Toxicology Studies," *Laboratory Animals* 33 (1999): 309–27.
7. T. L. S. Sprigge, "Philosophers and Antivivisectionism," *Alternatives to Animal Use* 13 (1985): 99–106, at 102–103.
8. See Pandora Pound and Michael Bracken, "Is Animal Research Sufficiently Evidence Based to Be a Cornerstone of Biomedical Research?" *BMJ* 348 (2014): 514–17; Jonathan Kimmelman and Alex John London, "Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty," *PLOS Medicine* 8, no. 3 (2011), <https://doi.org/10.1371/journal.pmed.1001010>, retrieved 19 June 2018.
9. See Rebecca Dresser, "Measuring Merit in Animal Research," *Theoretical Medicine* 10 (1989): 21–34.

The Mouse in the Room

The Critical Distinction Between Regulations and Ethics

Joseph P. Garner

What Ethics Gives Us: The Value of Beauchamp and DeGrazia's *Principles of Animal Research Ethics*

On a day-to-day basis the protection of laboratory animal welfare relies on a regulatory structure—from OLAW (the Office of Laboratory Animal Welfare) and other federal offices, to attending veterinarians, to the IACUCs (Institutional Animal Care and Use Committees). The existing regulatory structure is in many ways a complex balancing act designed to protect animals, enable meaningful science, and plug holes in the legislative framework. For instance, when the Animal Welfare Act nonsensically denied the same legal protections to rats and mice that it affords dogs, bats, and salamanders, the regulatory community quickly found a workable solution to this problem.¹

This simple example illustrates the difference between regulations and ethical principles. Regulations are rules we are required to follow, whether they make sense or not. We do our best to do the right thing within the constraints of their imperfection, but they are the reality on the ground. Ethical principles, by contrast, are abstract; they often do not clearly determine an answer, but rather exhibit the pros and cons of any possible decision.

Consequently, ethical principles frustrate those administrators and scientists who live and breathe by unambiguous answers.

Ethical thinking is often dismissed as a waste of time precisely because it doesn't provide a determinate answer or because it leads to "regulatory creep," as if we knew for certain that current regulations were enough to ensure the humane treatment of animals (or that humane treatment and ethical treatment were the same things). Beauchamp and DeGrazia, by outlining ethical principles in clear language, provide an invaluable bridge. They set our current regulatory system in an ethical framework, exposing both its strengths and weaknesses. The first half of this commentary argues for the value of this exercise; the second half provides case examples where applying these ethical principles actually empowers us to change how we approach current regulatory problems.

Regulations Constrain Choices; Ethical Principles Facilitate Moral Thinking

Beauchamp and DeGrazia correctly single out Russell and Burch's 1959 book, *The Principles of Humane Animal Experimentation*, which advanced the framework commonly referred to as the "Three Rs"² as the seminal document in the development of laboratory animal welfare standards, particularly with respect to U.S. law and regulation. Beauchamp and DeGrazia recognize the good done by the Three Rs, while also pointing out two unintended consequences of using them as a comprehensive framework.

First, Russell and Burch focus on welfare issues arising from the performance of experimental procedures and explicitly exclude from their discussion welfare issues arising from housing, husbandry, breeding, and all the other procedures and uses of animals that support the experiment itself. This focus has trickled down into current regulatory practice, which pays far more attention to the experimental procedures, even though the housing, husbandry,

and breeding systems involved make up the vast majority of the time, experience, and welfare of the animals themselves.³

Second, Russell and Burch's contribution is not an explicit discussion of ethical principles. Instead, the principles outlined in their book are essentially broad *regulatory* principles—directing us to Reduce, Refine, and Replace animal use—and a series of erudite suggestions for how to apply these directives. The trap that we risk falling into is to mistake these regulatory principles for *ethical* principles and to believe that the Three Rs encompass the full range of issues to consider with respect to laboratory animal welfare.

This point is illustrated by contrasting the Three-Rs approach with Beauchamp and DeGrazia's initial separation of their six ethical principles into "principles of social benefit" and "principles of animal welfare." This distinction is heuristically useful. For instance, biomedical research advocates will generally argue for the benefits of animal research in terms of the principles of social benefit, while animal protectionists will generally argue against animal research in terms of the principles of animal welfare. Thus, Beauchamp and DeGrazia show us how we talk past each other (see societal constructs of animal welfare as discussed by Fraser or Rollin),⁴ and establish these two different forms of argument as necessary and equal considerations in the same ethical framework rather than inherently alien to each other.

When the Right Thing to Do Is Not Always Obvious, We Need a Common Language to Discuss Ethical Decision-Making

As IACUC members and as researchers considering the ethics of a particular experiment, we find that our internal dialogue and decision-making can become conflicted in a similar way, and even sometimes feel insoluble. For example, consider an animal welfare scientist's proposed experiment testing whether there

are welfare benefits of housing animals in an enriched environment. At first sight, this seems innocuous and eminently justifiable. However such an experiment requires housing control animals in a standard environment that the experimenter believes is detrimental to welfare; and in reality animal welfare scientists are often motivated by the conviction that the status quo is morally questionable. There is a squeamishness to such experiments, even when the control is a seemingly innocuous status quo, as if the ends don't quite justify the means, or as if by focusing on the greater good we are missing something important about the animals themselves. Beauchamp and DeGrazia capture this sentiment neatly: "[S]entient animals have moral status and therefore are not merely tools of research. . . . In brief, sentient animals matter. . ." (pp. 2–3).

Thus, we can summarize the ethical dilemma of this hypothetical animal welfare scientist as follows: "We study suffering because alleviating it is good, and inflicting it is wrong. Yet we can't study suffering in an animal that can't suffer, and we can't study suffering without inflicting it." The same ethical conflict exists in many other areas of biomedical research. I can't test for analgesics (painkillers) in an animal model that cannot feel pain, I can't test antidepressants in animals that cannot be depressed, and the same goes for studies of fear, anxiety, panic, addiction, social function, or stress. In all these examples (and many more) the better the model, the more justifiable the experiment becomes according to the principles of social benefit, but by the same token, the greater the potential negative impact on animal welfare, the less justifiable the experiment becomes according to the principles of animal welfare. (Contrariwise, there is a strong case that better welfare conditions for animals generally lead to better scientific outcomes,⁵ but that is an empirical issue separate from the ethical point of this thought experiment.)

In a nutshell, this thought experiment captures the frustration that scientists have with ethical discussions. But how do we not

become paralyzed by this catch-22? And if we're unable to reach a resolution, what use is ethics anyway? For many researchers our exposure to ethics is limited to absolute rights and wrongs in terms of research conduct. By contrast the entire point of a set of ethical principles is *not* to dictate what is right but to give us a framework for understanding the moral implications of our decisions. The catch-22 just mentioned exists only if we insist on a prescriptive answer. Thus Beauchamp and DeGrazia's principles help us escape the trap of needing prescriptive absolutes and instead give us a common language with which to discuss the nuances of ethical scenarios in animal research. The importance of doing so is apparent in their discussion of the moral duties of IACUCs.

The Importance of IACUC Cultural Norms

IACUCs follow a complex set of guidelines and regulations that supplement the law governing animal use (including establishing IACUCs and their responsibilities).⁶ In this complex landscape, IACUCs individually, and as a community, have adopted certain cultural norms, particularly regarding their authority to ask researchers to change certain aspects of a proposed protocol. Generally speaking, the more a given issue is within the realm of veterinary care, the more likely an IACUC is to intervene. Without exception IACUCs would feel comfortable insisting on basic standards of aseptic technique in surgery, and almost all would insist on a particular standard of analgesia or anesthesia in the face of scientific objections. However, at the other end of the spectrum, very few would impose minimum requirements in terms of experimental design or statistical analysis (in direct contrast to an institutional review board regulating human research), despite evidence that doing so would have enormous benefits in light of Beauchamp and DeGrazia's principles,

particularly in terms of reducing sample size and unnecessary animal use.⁷

Despite IACUCs' reluctance to intervene with respect to these issues, the regulatory documents and law clearly give them equal authority both to require protocols to minimize pain and distress and to require protocols to minimize unnecessary animal use (e.g. through refined experimental design). Beauchamp and DeGrazia repeatedly emphasize that a particular ethical principle carries with it a moral obligation for the IACUC. In every case they are correct, and in many cases similar functional recommendations can be found in the *Guide* or in federal rules. For instance, OLAW clearly stipulates that an IACUC should assess the scientific merit of a proposal⁸—in other words, that an IACUC should consider the principles of social benefit and whether an improved experimental design or less invasive methods could achieve the same or better results. The only reason that some IACUCs are hesitant to pursue these issues is cultural. In direct contrast, Beauchamp and DeGrazia show us that doing so is ethically justified, if not mandated.

Where IACUCs Fear to Tread: The Ethical Argument for Overseeing More than Pain, Distress, and Aseptic Technique

The second half of this commentary focuses on three case studies where applying Beauchamp and DeGrazia's principles should lead an IACUC to consider issues that it might have (culturally) considered beyond its remit, but where the existing law and regulations do give it room to act. In other words, these are cases where ethical thinking should reasonably inform best practices that can be immediately implemented within the existing regulatory framework. In each case I suggest a best practice based on applying specific ethical principles.

The Ethical and Scientific Imperative to Enforce Standards in Experimental Design (Principles 2, 3, and 4)

A variety of regulatory documents, including the *Guide*, require that IACUCs assess whether a protocol has justified the number of animals proposed and whether appropriate steps have been taken to minimize animal use (in accordance with the Three-Rs principle of reduction). Many authors have argued that researchers should adopt basic established best practices in experimental design and analysis that do not just reduce animal use (consistent with Beauchamp and DeGrazia's Principle 4), but also minimize false discovery and maximize the likelihood of reproducibility and translation to humans (consistent with Principles 2 and 3 and the Three-Rs principle of refinement). At a bare minimum, such methodology would include blinding and other procedures to avoid bias, randomization of treatment allocation, randomization of environmental confounds, randomized block and factorial designs, and appropriate analytical procedures. None of these requires any additional experimental effort or animal use. In fact, they can actually reduce the number of animals needed to achieve power when properly analyzed.⁹

Poor experimental design and analysis are objectively major issues throughout human and animal research, with top journals reporting high rates of statistical errors in published papers (e.g., 38 percent in one case).¹⁰ In concordance, recent independent systematic reviews show that (for instance) only 13 percent of experiments were properly randomized and only 14 percent properly blinded (across a wide range of animal research disciplines);¹¹ and between 0 percent and 50 percent of factorial designs were properly analyzed (depending on the subdiscipline) within top neuroscience journals.¹² This level of statistical illiteracy is not just shocking; it has very real consequences with ethical implications. Thus, in a systematic postmortem of irreproducible studies, these

basic considerations of experimental design and analysis are the main predictors of whether a published result is replicable in an independent laboratory.¹³

The inflation of effect sizes in unblinded or unrandomized studies is widely recognized as a sign of unintended bias. There are many ways in which bias can influence data, even in the most well-meaning and rigorous experimenter, and only blinding and randomization can effectively protect against it.¹⁴ This is particularly true for measures where human judgment is involved (e.g., when one is reading histology slides or scoring behavior). Similarly, it is essential to randomize treatment allocation with respect to known and unknown nuisance variables. For instance, rack position is a major confound in mouse studies, with significant increases in stress, anxiety, abnormal behavior, and immune suppression in mice housed on top tiers of a rack.¹⁵ Thus, if all the treatment animals are housed on the top of the rack, and all controls on the bottom, then the entire experiment is potentially ruined. Randomization is particularly effective at mitigating these problems when the experiment is properly analyzed (e.g., as a randomized block design) and is easily implemented in the laboratory.¹⁶ These and other improvements in study design would afford a greater chance that animal studies will be able to meet the cost-benefit requirements of Beauchamp and DeGrazia's Principles 2 and 3.

The larger the effect size, the more likely an experiment is to detect it (that is, the more powerful the experiment is). Effect size in statistics (and thus power) is typically a signal-to-noise ratio. Animal experiments tend to improve signal-to-noise through the brute-force method of increasing sample size, which is progressively *less* efficient as sample size increases for simplistic analyses like a T-test. Human experiments use more sophisticated methods such as randomized block designs to reduce noise without increasing sample size. These methods exploit the fact that there are different kinds of noise (unexplained random noise and predictable

noise from nuisance variables), which behave differently with respect to sample size. Including nuisance variables in the analysis is progressively *more* efficient in reducing the influence of random noise as sample size increases, so that increasing sample size rapidly has no additional benefit. For small signals this can lead to orders of magnitude differences in necessary sample size between a naive design and T-test and a “human design” and F-test.¹⁷

Thus, while the reproducibility and translatability crises are real, they’re not the insoluble crises portrayed by many anti-research activists. We understand how lax experimental design and analysis actively create irreproducible results, we understand many of the sources of poor translation, and we know which basic standards in experimental design and analysis resolve these issues.¹⁸ Thus, resolving the reproducibility and translatability crises, consistent with Principles 2 and 3, is a matter of changing minimal best practice in experimental design and analysis. As such it should be a basic responsibility of an IACUC to ensure that minimal best practices are followed. However, few IACUCs have a statistician as a standing member, whereas, by contrast, all have a veterinarian. How then can the level of experimental design oversight be brought up to the standard of veterinary oversight?

One way to promote best practices and detect problematic protocols is to require a data analysis plan (as is required for human drug trials). The NC3Rs of the UK’s Medical Research Council provide the “Experimental Design Assistant” (EDA),¹⁹ an online tool for planning experiments and preparing a data analysis plan, including checks for randomization, blinding, nuisance variables, and appropriate analyses. As researchers should be going through these steps in designing a protocol, it is no burden to submit a formal analysis plan (and one benefit of the EDA is that it produces standardized reports, making it easy for an IACUC to assess the experimental design). Often, even well-designed experiments hit obstacles when it comes to data analysis. It is therefore wise to also perform (and submit to the IACUC) analyses of mocked-up data

ahead of time. This helps the experimenter see issues in the fine details of the experiment and its analysis. Generating the mock data also requires the experimenter to think about expected effect sizes and alternative hypotheses. Mock analyses also allow the IACUC to better understand the experimental design, as well as the assumptions behind power and numbers justifications, and to identify experiments where animal use could be reduced by a more efficient (e.g., factorial) design.

The Ethical and Biological Imperative for Environmental Enrichment (Principles 2, 3, 4, and 5)

Environmental enrichment is arguably the paradigm example of “good welfare is good science.” The underlying biological argument is straightforward and has been made many times elsewhere. Briefly, animals respond to stressors (homeostatic challenges) with autonomic, neuroendocrine, immune, and behavioral defenses. But of all these responses, behavior is by far the most important—a thirsty plant dies, while a thirsty animal walks to water. In other words, the distinctive characteristic of animals among living things is to behave, and the purpose or goal of behavior is to provide prediction and control over stressors that mere physiology cannot handle. Control is so central to animals that animals without control, even over non-life-threatening stressors, will employ every tool they have—autonomic, neuroendocrine, immune, and behavioral—to the point of system failure. While operational definitions of enrichment may emphasize natural behavior, or the absence of abnormal behavior, I and others have argued that any biologically relevant enrichment must provide control over a stressor. Control is not only biologically critical, but ethically central. It doesn’t matter which view of welfare (health, avoiding suffering, or living according to one’s nature) one holds, all such views intersect

at control. The power of focusing on control is that it circumvents the otherwise stifling crosstalk about what welfare is—control is the one thing on which all visions of welfare can agree.²⁰ Enrichment can provide direct control over a stressor by providing a physical substrate required for behavior (e.g., nesting material); or, more subtly, enrichment can also provide control by allowing animals to buffer stressors with nonspecific coping strategies (i.e., increase their “coping capacity,” e.g., via social support).

Nesting material in mice is arguably the most thoroughly evidenced example of “biologically relevant enrichment” (largely thanks to B. N. Gaskill) and is now widely implemented. In contrast, social housing of rodents is still a matter of controversy, but nevertheless provides a clear-cut example of the benefits of control and “good welfare is good science.” In many areas of palliative care in humans, the quality of social networks has a direct impact on health outcomes. A particularly striking example is breast cancer, where the cumulative effects of different positive social relationships can account for more than fiftyfold improvements in survival in humans. Exactly the same benefits of social support can be seen in cancer models in both rats and mice.²¹ The irony is that many researchers would dismiss social housing as a confound or “source of variation,” when in fact it is not just clinically relevant, but also a means to study the mechanism of a palliative care effect that is as impactful as many medical interventions.

Researchers often object to enrichment because it will change the model with respect to historical controls. But this argument is a straw man, for two reasons. First, there is no such thing as a historical control in practice: from year to year (if not month to month) countless changes occur in a vivarium (from diet, to caging systems, to handling protocols, to animal care staff), and thus a contemporaneous control is required for every experiment. Accordingly no journal would accept a paper in which the control group was historical (nor should an IACUC), not just as a matter of good science but also as a matter of complying with principles of social benefit.

Second, if enrichment is biologically relevant, it *should* change the model; the animals should be better models of humans. Not all change is bad, and in this case change is definitely good. If a model “stops working” in enriched animals, then it has shown a lack of generalizability, particularly to animals that are more like human patients, and therefore is a likely candidate for false discovery, lack of reproducibility, and lack of translation. Models should be robust and reproducible across multiple environments—if not, the problem is not with enrichment but with a bad model.

Thus, Beauchamp and DeGrazia help us see that the enrichment-will-change-the-model argument is deeply problematic. Enrichment is mandated by both the principles of social benefit and the principles of animal welfare. By contrast, a model that “works” only in barren housed animals is of little social benefit and a concern in terms of animal welfare. Thus, the enrichment-will-change-the-model argument is not just antithetical to good science; it is essentially unethical and should be rejected by an IACUC as such.

Furthermore, changes in models in response to enrichment can recapitulate real-world effects in humans. In other words, enrichment itself can be a model. For instance, aside from the effects of social support on cancer, enrichment models the protective effect of intellectual challenge against neurodegenerative disease in humans. As medical research increasingly focuses on early detection and prevention, what could be more valuable than a model that recapitulates such effects and offers the opportunity to study them in animals with two- to three-year life spans? This conception of animal models as time machines that let us tease out developmental effects, identify screening biomarkers, and identify preventative interventions is the real cutting edge of personalized medicine and biomedical research.²²

In terms of best practice for IACUCs, enrichment should be the norm, not the exception for all species—the basic biology of stress and control applies equally to zebrafish as it does to mice. However, enrichment should be evidence-based, and an emphasis placed on

control (recognizing the paucity of the available literature). Social support is particularly important for species that benefit from it and should be provided, particularly when the goal of the experiment is to model human disease. Finally, enrichment-will-change-the-model arguments should be recognized as unethical. At the very least IACUCs should place the burden of proof on researchers who wish to withhold enrichment (just as an IACUC would expect a researcher wishing to withhold analgesia to demonstrate that it was absolutely necessary to do so). In other words, IACUCs should be prepared to take enrichment-will-change-the-model arguments as grounds for asking researchers to justify the validity of their model in the first place.

The Ethical Imperative to Proactively Question Established Procedures (Principles 4, 5, and 6)

Many commonly used procedures carry potential harms, bringing the principles of animal welfare into play. Many also present challenges in terms of reproducibility, translatability, or validity (i.e., they have questionable benefits in terms of the principles of social benefit).²³

Consider a recent study, in which researchers were interested in “crowd emergency evacuation” behavior.²⁴ There is obvious societal benefit in understanding how humans might behave escaping from such situations. The researchers investigated this problem by dropping mice in a pool of water with two points of escape and studying group sizes of up to thirty mice using a variety of automated tracking programs that provided a wealth of objective data without the researchers actually having to watch the animals in question. While this study may appear innocuous, the videos provided as supplementary information tell a different story. Mice can be clearly seen unable to keep their heads above water throughout the procedure. I regularly show these videos during talks to

IACUCs and scientific audiences, and without exception the audience members are upset and outraged. I often ask those present whether they would approve the experiment if they had seen pilot data that included the video (rather than the video tracking data presented in the main paper), and without exception the answer is a hard “no”. However, this experiment is simply a variant on other water-escape procedures approved by IACUCs without question on a routine basis. The reality is that many of those outraged and upset audience members have themselves approved procedures in which mice are exposed to similar escapable (or inescapable) pools of water, with similar stressors and behavioral reactions.

The preceding example is easy to understand because we begin with a severe case and work back to its general implications. It illustrates the need for IACUCs to be vigilant about welfare concerns in commonly accepted procedures, but it doesn’t provide much guidance for detecting such issues in day-to-day deliberations. Instead, let us consider an issue that is flagged by the *Guide* but would not appear on the radar of many IACUCs because it is such an established status quo, namely water deprivation. There *is* considerable debate over the use of water deprivation as a motivator in cognition experiments.²⁵ Water rewards are very convenient and can be easily administered to animals that need to be restrained. They are also easy to dispense, and dispensing apparatus is much easier to keep sterile. The principle of no unnecessary harm and the principle of basic needs help us see that such convenience is irrelevant and that water deprivation is unethical if other, less invasive methods are available.

In response, proponents of water deprivation argue that it is necessary because more complex tasks require higher motivation and thus more severe deprivation. This is not only incorrect but counterproductive in terms of frustration and overall task motivation. Thus, consider an animal presented with a complex, if not seemingly insoluble task, and how that animal might respond if she was comfortable and the reward was a treat, versus if she was restrained and

thirsty and the reward was water. What experimenters advocating for water deprivation as a motivator ignore is that in both cases the payout for a correct response is positive, but in deprived animals the negative consequences of an incorrect response are far greater. While the animal does not understand the task (which by definition lasts longer in the earlier stages of more complex tasks), the affective experience of performing the task is far more frustrating for a deprived animal. As a result, the experience of performing the task in general is negative, and animals are much less likely to be compliant or willing to take part in the task in the first place.

Conversely, less invasive methods are easy to imagine. Anyone who has trained a dog to sit or not to jump on the couch knows this is possible without depriving the dog of food or administering an electric shock. Simple alternatives are available to laboratory animal researchers. For instance, most animals have natural periods of fasting (while they sleep) and corresponding natural periods of high motivation for foraging and food reward. It is practically very easy to withhold food while animals are asleep and to exploit their natural drive for food early in their day. For instance, by applying these and other principles of naturalistic task design, we were able not only to train mice on a complex cognitive task where previous authors had failed (and argued that mice were cognitively incapable of such a task), but also to obtain levels of task performance comparable to that of primates. This general approach is even more powerful when coupled with automated environments. For instance, by presenting a different complex task as an automated foraging problem in the home cage, we were able to obtain higher-quality data far faster from the same animals than when we used traditional deprivation and maze-based methods.²⁶

These examples suggest a simple standard: IACUCs should observe the proposed procedures before they approve them. IACUCs often require that veterinary staff attend surgeries to ensure aseptic technique and appropriate analgesia and anesthesia before a protocol is approved. The same level of oversight should exist for all

procedures, from the Morris water maze to forced swim tests, to tail flick and hotplate tests, to the response of water-deprived animals to rewarded and unrewarded trials, and to home-cage videos of animals with tumor burdens or surgical interventions. If researchers have a serious commitment to animal welfare, they should be unfraid to provide videos of their procedures to the IACUC.

Closing Comments

Hopefully my commentary has illustrated how Beauchamp and DeGrazia's ethical principles stand to reinforce our current regulatory system, while challenging us to apply a consistent level of ethical thinking and to reexamine current inequities and inconsistencies in our regulatory practice. More simply, the value of ethical principles is that they keep us honest. Even if the right thing to do is not always obvious, at least we now have a common language to discuss these issues and a framework within which we can prioritize areas that urgently need change, make such changes as practice evolves, and question the status quo whenever appropriate.

Notes

1. See Animal Welfare Institute, awionline.org/content/rats-mice-birds, and www.nabr.org/are-research-rats-mice-and-birds-protected-species/, retrieved 12 November 2018.
2. W. M. S. Russell and R. L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).
3. National Research Council (U.S.), Committee for the Update of the Guide for the Care and Use of Laboratory Animals, *Guide for the Care and Use of Laboratory Animals*, 8th ed. (Washington, DC: National Academies Press, 2011), www.ncbi.nlm.nih.gov/books/NBK54050/, retrieved 12 November 2018. The *Guide* covers housing and husbandry in detail, but this area of protection is often not the focus of IACUC reviews of a protocol.

4. For overview see I. J. H. Duncan and D. Fraser, "Understanding Animal Welfare," in M. C. Appleby and B. O. Hughes (eds.), *Animal Welfare* (Wallingford: CABI, 1997), 19–31. For Rollin in the context of laboratory animals, see C. Foltz, L. Carbone, D. DeLong, B. E. Rollin, P. Van Loo, J. Whitaker, and A. Wolff, "Considerations for Determining Optimal Mouse Caging Density," *Lab Animal* 36, no. 10 (November 2007): 40–49.
5. J. P. Garner, B. N. Gaskill, E. M. Weber, J. Ahloy-Dallaire, and K. R. Pritchett-Corning, "Introducing Therioepistemology: The Study of How Knowledge Is Gained from Animal Research," *Lab Animal* 46, no. 4 (March 2017): 103–13; B. N. Gaskill and J. P. Garner, "Stressed Out: Providing Laboratory Animals with Behavioral Control to Reduce the Physiological Effects of Stress," *Lab Animal* 46, no. 4 (March 2017): 142–45.
6. The *Guide* summarizes the law, federal agencies, and various regulatory documents. For the authoritative overview of current implementation and regulations in the United States, see *PHS Policy on Humane Care and Use of Laboratory Animals*, as revised 28 November 2017, olaw.nih.gov/guidance/faqs, retrieved 12 November 2018.
7. Many authors have emphasized the central importance of experimental design to translation (i.e., principles of social benefit) and to minimizing animal use (i.e., principles of animal welfare). See J. P. Garner, "The Significance of Meaning: Why Do Over 90% of Behavioral Neuroscience Results Fail to Translate to Humans, and What Can We Do to Fix It?" *ILAR Journal* 55, no. 3 (January 2014): 438–56; M. F. W. Festing, "Randomized Block Experimental Designs Can Increase the Power and Reproducibility of Laboratory Animal Experiments," *ILAR Journal* 55, no. 3 (2014): 472–76; C. G. Begley, "Six Red Flags for Suspect Work," *Nature* 497, no. 7450 (May 2013): 433–34; and S. H. Richter, J. P. Garner, C. Auer, J. Kunert, and H. Würbel, "Systematic Variation Improves Reproducibility of Animal Experiments," *Nature Methods* 7, no. 3 (2010): 167–68.
8. *PHS Policy on Humane Care and Use of Laboratory Animals*, D. Protocol Review, No. 12, "Is the IACUC Responsible for Judging the Scientific Merit of Proposals?," olaw.nih.gov/guidance/faqs#628, retrieved 12 November 2018.
9. See note 7.
10. Editorial, "Statistically Significant," *Nature Medicine* 11, no. 1 (January 2005): 1.
11. C. Kilkenney, N. Parsons, E. Kadyszewski, M. F. W. Festing, I. C. Cuthill, D. Fry, J. Hutton, and D. G. Altman, "Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals," *PLOS ONE* 4, no. 11 (2009): e7824.

12. S. Nieuwenhuis, B. U. Forstmann, and E.-J. Wagenmakers, "Erroneous Analyses of Interactions in Neuroscience: A Problem of Significance," *Nature Neuroscience* 14, no. 9 (2011): 1105–107.
13. Begley, "Six Red Flags for Suspect Work."
14. For an example of a meta-analytic study, see J. A. Hirst, J. Howick, J. K. Aronson, N. Roberts, R. Perera, C. Koshariis, and C. Heneghan, "The Need for Randomization in Animal Trials: An Overview of Systematic Reviews," *PLOS ONE* 9, no. 6 (2014): e98856. For further discussion see N. Percie du Sert et al., "The Experimental Design Assistant," *PLOS Biology* 15, no. 9 (2017): e2003779.
15. For examples of the impact of cage position as a nuisance variable, see D. N. Ader, S. B. Johnson, S. W. Huang, and W. J. Riley, "Group-Size, Cage Shelf Level, and Emotionality in Nonobese Diabetic Mice: Impact on Onset and Incidence of IDDM," *Psychosomatic Medicine* 53, no. 3 (1991): 313–21; and J. P. Garner, B. Dufour, L. E. Gregg, S. M. Weisker, and J. A. Mench, "Social and Husbandry Factors Affecting the Prevalence and Severity of Barbering ('Whisker Trimming') by Laboratory Mice," *Applied Animal Behaviour Science* 89, no. 3–4 (2004): 263–82.
16. See H. Würbel and J. P. Garner, "Refinement of Rodent Research Through Environmental Enrichment and Systematic Randomization," *NC3Rs* 9 (2007): 1–9; and Garner, "The Significance of Meaning."
17. See Garner, "The Significance of Meaning," for a simulated example of this effect.
18. See the preceding references citing Garner and coauthors, Würbel and coauthors, and Begley. For a comprehensive summary, see Garner et al., "Introducing Therioepistemology."
19. The NC3Rs Experimental Design Assistant can be found at www.nc3rs.org.uk/experimental-design-assistant-eda, retrieved 12 November 2018; Percie du Sert et al., "The Experimental Design Assistant."
20. Key references in this literature include Würbel and Garner, "Refinement of Rodent Research Through Environmental Enrichment and Systematic Randomization"; Gaskill and Garner, "Stressed Out: Providing Laboratory Animals with Behavioral Control to Reduce the Physiological Effects of Stress"; G. P. Moberg, "Biological Response to Stress: Implications for Animal Welfare," in G. P. Moberg and J. A. Mench (eds.), *The Biology of Animal Stress: Basic Principles and Implications for Animal Welfare* (Wallingford: CABI, 2000), 1–22; J. M. Weiss, "Effects of Coping Behavior with and without a Feedback Signal on Stress Pathology in Rats," *Journal of Comparative and Physiological Psychology* 77, no. 1 (1971): 22; and

- B. N. Gaskill, K. R. Pritchett-Corning, C. J. Gordon, E. A. Pajor, J. R. Lucas, J. K. Davis, and J. P. Garner, "Energy Reallocation to Breeding Performance through Improved Nest Building in Laboratory Mice," *PLOS ONE* 8, no. 9 (2013): e74153.
21. C. H. Kroenke, L. D. Kubzansky, E. S. Schernhammer, M. D. Holmes, and I. Kawachi, "Social Networks, Social Support, and Survival after Breast Cancer Diagnosis," *Journal of Clinical Oncology* 24, no. 7 (March 2006): 1105–11; L. R. Kerr, M. S. Grimm, W. A. Silva, J. Weinberg, and J. T. Emmerman, "Effects of Social Housing Condition on the Response of the Shionogi Mouse Mammary Carcinoma (Sc115) to Chemotherapy," *Cancer Research* 57, no. 6 (March 1997): 1124–28; G. L. Hermes, B. Delgado, M. Tretiakova, S. A. Cavigelli, T. Krausz, S. D. Conzen, and M. K. McClintock, "Social Isolation Dysregulates Endocrine and Behavioral Stress While Increasing Malignant Burden of Spontaneous Mammary Tumors," *Proceedings of the National Academy of Sciences of the United States of America* 106, no. 52 (December 2009): 22393–98.
 22. My coauthors and I have argued that the true value of animal models is enabling personalized preventative medicine (Garner et al., "Introducing Therioepistemology.") For specific examples of animals revealing developmental biomarkers, see K. J. Parker et al., "Arginine Vasopressin in Cerebrospinal Fluid Is a Marker of Sociality in Nonhuman Primates," *Science Translational Medicine* 10, no. 439 (2018); and G. L. T. Vieira, A. C. Lossie, D. C. Lay, Jr., J. S. Radcliffe, and J. P. Garner, "Preventing, Treating, and Predicting Barbering: A Fundamental Role for Biomarkers of Oxidative Stress in a Mouse Model of Trichotillomania," *PLOS ONE* 12, no. 4 (2017): e0175222.
 23. Garner et al., "Introducing Therioepistemology."
 24. Caesar Saloma, Gay Jane Perez, Catherine Ann Gavile, Jacqueline Judith Ick-Joson, and Cynthia Palmes-Saloma, "Prior Individual Training and Self-Organized Queuing During Group Emergency Escape of Mice from Water Pool," *PLOS ONE* 10, no. 2 (2015), <https://doi.org/10.1371/journal.pone.0118508>, retrieved 12 November 2018.
 25. H. Gray, H. Bertrand, C. Mindus, P. Flecknell, C. Rowe, and A. Thiele, "Physiological, Behavioral, and Scientific Impact of Different Fluid Control Protocols in the Rhesus Macaque (*Macaca mulatta*)," *eNeuro* 3, no. 4 (July–August 2016), www.ncbi.nlm.nih.gov/pmc/articles/PMC5032891/, retrieved 12 November 2018.
 26. J. P. Garner, C. M. Thogerson, H. Würbel, J. D. Murray, and J. A. Mench, "Animal Neuropsychology: Validation of the Intra-Dimensional

Extra-Dimensional Set Shifting Task in Mice,” *Behavioural Brain Research* 173, no. 1 (2006): 53–61; E. Y. Pioli, B. N. Gaskill, G. Gilmour, M. D. Tricklebank, S. L. Dix, D. Bannerman, and J. P. Garner, “An Automated Maze Task for Assessing Hippocampus-Sensitive Memory in Mice,” *Behavioural Brain Research* 261 (March 2014): 249–57.

Compassion for Other Animals Beyond the Human Hierarchy of Concern

Brian Hare

Everyone has heard of the dog suffering under vivisection, who licked the hand of the operator; this man, unless the operation was fully justified by an increase of our knowledge or unless he had a heart of stone, must have felt some remorse to the last hour of his life. (Charles Darwin, *Descent of Man*)¹

I love our dogs as members of our family, but unlike with my children, it is hard to imagine a scenario where I would intentionally give my life for them. I also would not hesitate to sacrifice our dogs to save my children and would stop my children from sacrificing themselves to save the dogs. These are unpleasant choices to consider, but the hierarchy of concern is clear and unsurprising. Our psychology has evolved to favor the well-being of our in-group, kin, and especially our offspring over that of others. However, this hierarchy of concern does not rule out care for others. Humans can show extraordinary compassion for strangers, out-groups, and even animals.² My preference for my children over our family's dogs does not stop me from showing extraordinary love for both.

I take pleasure in bringing joy to our dogs' lives while preventing even the smallest amount of suffering. This motivation also extends to other animals that are not part of my family. I brake for a squirrel or stop my car to help a turtle in the road. I lobbied to end invasive testing on chimpanzees and work to end the illegal bushmeat trade threatening our other ape relatives with extinction. I have even moved drowning worms out of puddles. So while I would sacrifice the dogs in favor of saving my children, I also would never knowingly promote or tolerate pain inflicted on any human or animal unless it was well justified.

I doubt I am different from most parents who have dogs since humans have a tremendous capacity to show compassion for those beyond their own kin. Yet when the ethics of invasive animal research is publicly debated, animals and humans are depicted as if they were rated on a single dimension of worth or moral status. People are caricatured as either ranking humans higher than animals or ranking animals equal to or higher than humans. This false dichotomy then determines if you are grouped among those who favor harming animals in order to help humans or among those who oppose harming animals even if not harming them might hurt humans. The best marketing brochures and political slogans on either side leave no room for the nuances of reality. This marketing characterizes people for or against invasive animal research as inhumane or even nonhuman. It suggests that a major share of financial resources to improve animal welfare (beyond providing basic needs) has gone into scoring points against the other side.

In the real world of research involving animals, there are compassionate people who harm animals to improve medicine for both people and animals while they try to ensure that the pain inflicted is minimized and justified. There are also people working outside research institutions who scrutinize efforts to reduce animal suffering. They are motivated to help animals, but often their critiques are also motivated by the goal of improving research outcomes for the betterment of humans. However, because this reality is

typically ignored in favor of the most polarizing examples, progress in objectively recognizing, reducing, and justifying pain in other animals has been limited. As Charles Darwin's observation suggests, confronting animal suffering caused by research is not a new problem, but efforts to significantly reduce harm may require new approaches that go beyond relying on caricatures, false dichotomies, and intergroup psychology in public debates on how to improve invasive animal research.

In this volume, Beauchamp and DeGrazia provide a moral framework meant to enhance the well-being of research animals—and thus animal research. While they recognize that research institutions have acknowledged the core values of animal research ethics, they suggest that without more explicit statements of how social benefits and animal welfare are or should be conceptualized, it remains difficult to morally justify invasive forms of animal research. They offer six principles that they argue any reasonable person would accept as conditions that must be satisfied for invasive animal research to be justifiable. They see each of these principles as individually necessary for the justification of invasive research, but they leave the possibility open that they are not jointly sufficient to justify some forms of research. Three of these principles spell out the social benefits necessary to justify causing harm, while the final three are designed to help guide decisions about causing suffering by placing restrictions on permissible harms to animal subjects.

Current review procedures for Institutional Animal Care and Use Committees (IACUCs) in the United States are already intended to evaluate proposed research based on whether pain or suffering is necessary, whether certain basic needs will be met (e.g., food, water, a pathogen-free environment), and whether alternative approaches are available.³ How successful the review process is in meeting these goals is debatable. Macaques generally do not need to be restrained for behavioral and cognitive work, yet the majority of researchers who use chairs to restrain monkeys do this for the purpose of behavioral and cognitive research that can last for

four to six hours each day.⁴ University IACUCs' rejection of some researchers' attempts to join the recent explosion in noninvasive, on-campus research involving pet dogs suggests that concerns about welfare are not always primary in the minds of welfare committee members. My conversations with investigators whose protocols were rejected revealed that some were told their protocol could be more easily accepted if they purchased and studied laboratory dogs (who would be euthanized at the end of the study period) instead of studying pets owned by volunteers.

The challenge of assessing research based on whether the pain it causes is necessary, whether basic needs are met, and whether alternatives are available also exists at the federal level in the United States. In debates over the future of federally funded chimpanzee laboratories, it was repeatedly stated that *all* chimpanzee research would end if labs funded by the National Institutes of Health (NIH) closed.⁵ This was patently false, as alternative sites had already been developed that provided access to better samples of subjects, required far less funding, benefited the species being studied, and proved more productive in health-related research.⁶ These types of stories make the pronouncement of most of the principles advanced by Beauchamp and DeGrazia redundant but essential. They give individual researchers the ability to challenge committee and institutional decisions based on moral grounds that have been explicitly laid out.

The most novel contributions of Beauchamp and DeGrazia are the principles stating the need to explicitly define upper levels of acceptable harm as well as to specify the expected net benefit of invasive animal research protocols to human health.

In the United States and many other countries, neither grant applications nor institutional review committees require explicit operationalization or justification of the acceptable upper level of pain. The emphasis instead is on the need to explain how painful procedures will be carried out to minimize suffering. Procedures perceived as the most painful are generally supposed to require the

most thorough justification. For example, making an exception to standards of basic care so that an animal may be killed without the use of an analgesic should require a more thorough justification than does briefly withholding water. But stating the appropriate upper level of pain for each new protocol is not required as long as pain levels will be within the bounds of what a committee considers normal. What is accepted as normal is in part highly subjective and often the result of the culture of the committee. Having researchers agree on standards that apply across institutions, explicitly state and evaluate the upper level of pain that is acceptable, and specify how surpassing the limit will be avoided and detected seems an obvious step in reducing unnecessary harm.

The principle of net benefit disallows the moral justification of invasive research based on the potential for scientific discovery for its own sake. Instead, Beauchamp and DeGrazia suggest that a calculation of social benefit is necessary that includes accounting for opportunity costs associated with the potential failure of invasive animal research to deliver actionable results that benefit humans (or, at the very least, extremely important knowledge). This suggestion rejects the commonly presented false choice of either curing disease by hurting animals or hurting people by prohibiting invasive medical work. The reality is that for each funded invasive animal study there are other studies using different research techniques that were not funded. Funding ineffectual research approaches can significantly slow progress in areas that will lead to success. It was more than fifteen years after the end of almost all HIV/AIDs testing on chimpanzees that the NIH cut funding to support the massive captive colonies of chimpanzees bred for HIV/AIDs vaccine testing.⁷ This funding of ineffectual research represented tens, if not hundreds, of millions of dollars that could have been more effectively spent on health research that had demonstrated benefits. Instead, aging and exorbitantly expensive infrastructure was maintained for a research program that a vast majority of researchers saw as having little or no medical value. The principle of net benefit was violated

in this case because anticipated costs exceeded any reasonable estimation of prospect of benefit. This cost–benefit failure is also part of the justification for NIH’s decision to finally end funding for all new medical research with chimpanzees.⁸ This also means that the delay in closing chimpanzee laboratories violated the principle of sufficient value, since a net benefit must be demonstrated as a precondition of being considered of sufficient value to justify harm. This new calculus will help institutions more quickly resolve future cases.

Beauchamp and DeGrazia have succeeded in providing a useful moral framework and argue convincingly that their principles move beyond the limitations of the time-tested Three-Rs model. As the authors suggest, though, their model is not without limitations. The most important limitations involve assumptions about human psychology. While many people can be reasonable in recognizing the logic of the authors’ six principles, some may not be reasonable when it comes to the perception of pain in animals. We surveyed a large sample of adults about pain sensitivity in different dog breeds.⁹ Participants rated larger dogs as less sensitive to pain than smaller breeds. Dogs with a dark coat color were rated as experiencing less pain than dogs of the same breed with light-colored fur. Dogs targeted by breed-specific legislation (e.g., pit bulls) were rated as experiencing less pain as well.

These patterns cannot be attributed to levels of experience or expertise with pain in dogs. Veterinarians as well as the general public showed similar patterns even though there is no evidence that different dog breeds have different neurobiology relating to pain sensitivity. Perceiving different pain sensitivities across dog breeds likely leads veterinarians to misdiagnose illnesses and misprescribe analgesics. It remains exceptionally difficult for even the best-trained staff to overcome biases, like the ones we have shown in dogs, when trying to assess pain in animals. Based on our veterinary results, where the veterinarians held some of the most extreme views about differences in pain sensitivity across dog breeds, it is

also likely that veterinary training itself introduced or enhanced misperception of pain in animals (echoing a similar phenomenon in human medicine). What predicted whether veterinarians had beliefs about differential pain sensitivity in dog breeds was not when they were trained, but only if they had been trained.

The problem is also much bigger than bias.¹⁰ Our psychology is designed with an off switch for mental state attribution. We dehumanize other humans in favor of our kin and in-group. Dehumanization is the result of inactivity in the brain's social network that allows for mental state attribution.¹¹ It allows for moral exclusion or a type of "moral blindness," and it occurs as a prelude to the worst forms of human aggression. Likewise, the objectification of animals is thought to tap into the same mechanism and open an avenue to inflicting harm.¹² Describing laboratory primates as aggressive is common practice—including within institutional online training activities.¹³ The intention is to make researchers cautious, but it likely encourages objectification and the moral exclusion of animals who are simply showing an adaptive response in an environment where they have little control. Humans are also less likely to attribute mental states and other human-like attributes to smaller, less human-like animals. Labeling individuals with numbers instead of names also reduces empathetic responses in the brain and behaviorally.¹⁴ These biases and objectification limit our perception of pain in others that in part drives compassionate behavior. Without a robust research program dedicated to how humans perceive pain in animals and how pain can be objectively measured, it will be difficult to meet the moral obligations of the six principles (especially the need to define upper limits of pain).

The six moral principles also do not seem to acknowledge the ecology of animal well-being.¹⁵ Animals have evolved to perceive, think, and feel in a variety of ways. Contrary to the model species approach, which assumes that phenotypic traits are widely and uniformly conserved, psychology can evolve rapidly to promote survival and reproduction in unique ecologies.¹⁶ These differences are

expressed in different behavioral preferences that can be counter-intuitive or even imperceptible to humans.¹⁷ They also vary wildly across species. A glaring example of the ecology of well-being is the mountain of biological evidence showing that domesticated animals suffer less in captivity than wild animals do,¹⁸ yet they receive identical treatment in current welfare policy. While the six principles address basic needs, including those for “species-typical functioning” and “access to compatible conspecifics or social group members,” the underlying assumption is that researchers or IACUCs can comprehend and estimate degrees of animal pain and preferences with some accuracy. This assumption may often be violated, as seen in the absence of a distinction in policy between wild and domesticated animals.¹⁹ This disconnect is likely to only grow as the use of experimental genomic techniques fueled by the use of CRISPR, cloning, and other gene editing tools accelerates. Populations of animals will be created that suffer in unique ways, but this suffering will be unknown until these populations are created and careful research is dedicated to finding means to measure and limit it. For example, in China, lines of beagles have already been created with genomes into which genes implicated in human autism have been inserted with the intention of creating autistic dogs. No research can predict how badly these dogs will suffer or how to reduce their suffering before they are created. These new technologies, in particular, stretch existing approaches to welfare and ethical codes of research as a result.

Beauchamp and DeGrazia take up the challenge of defining the type of research that would need to meet the moral criteria they spell out. This includes animal research where the animals have no control, cannot provide formal consent, and do not benefit as individuals from participation. They suggest that nearly all animal research can cause nontrivial harm to its subjects. These criteria can be broadly interpreted to apply to research that I might categorize as noninvasive. When I play cognitive games with dogs, I am in control since I have a leash and treats, the dogs cannot give

formal consent before the study begins, and there is not necessarily a health *benefit* for individual dogs. This might suggest that these criteria for invasiveness need further refinement. A shift to focus on research that causes significant harm to an individual and does not allow for voluntary participation (as opposed to formal consent) might better target research that is most likely to be invasive. Most animals are capable of indicating behaviorally that they do not want to participate in an activity. While I cannot obtain formal consent from bonobos, I also cannot force them to play cognitive games. This is especially the case when these animals are not food- or water-restricted. They are capable of indicating their lack of interest in participating by sitting near the exit of the test room, not eating the rewards, or showing stress behaviors like heavy scratching.

Any of these behaviors can be operationalized to indicate that an experiment should be ended. Moreover, animals can also be trained to volunteer for both noninvasive and invasive procedures.²⁰ A number of species kept in zoos and sanctuaries have been trained to voluntarily sit without stress while blood samples or vital signs are taken, cortical activity is measured, or ultrasounds are administered.²¹ Again, these animals choose to participate in order to receive food and social rewards, even though the managers control the training environment that leads to the development of this preference.

In calculating the moral basis of invasive animal research the authors also do not seem to factor in how invasive medical work can have a positive impact on animal health and well-being. For example, invasive techniques may be necessary to improve objective measures of suffering across different species.²² This research will often be ethically challenging since it may require *causing* the pain to be measured and prevented. Without such work it may be extremely difficult to implement the six principles based on objective measures of welfare. The six principles also appear to be silent on the ethics of research that might require invasive animal research for the purpose of saving a population of animals,

including those that are endangered—for example, Ebola vaccine trials on chimpanzees for the purpose of proving that the vaccine can be used to save wild ape populations or cloning and genomic techniques being developed for de-extinction experiments.²³ All of these examples challenge the definition of what should or should not be considered invasive and also how to determine whether particular invasive studies are morally defensible.

Even with these limitations, Beauchamp and DeGrazia have done a great service in making a convincing case for these six moral principles. It might be expected that we humans have an intuitive sense of how animals should be treated morally, but increasingly we see evidence that context powerfully shapes when and if we apply moral reasoning. The fact that our brains are capable of morally excluding members of our own species should make obvious the need for this type of moral guidance in work with other species.²⁴ The context of laboratory research in particular is one in which we cannot depend on moral intuitions to guide welfare decisions. The scale of most research laboratories works against compassion. Large populations of medical research animals are known by tattoo numbers instead of by names of recognizable individuals. Emphasis on the potential for zoonotic disease transmission, personal protective equipment, and the need for sterile conditions also encourages emotions of disgust toward lab animals. This can promote objectification and squelch the potential for compassion—especially toward small, nameless, object-like individuals.²⁵

If we are to continue using animals in invasive medical research, we need clear moral guidance that can inform both policy and research on how we can reduce suffering and advance health for both humans and animals. Beauchamp and DeGrazia have made an important step in helping shape how we can recognize when invasive research should be allowable or not. The limitations of their model also help clarify where future research will be needed to better detect and reduce pain and suffering in animals. The public will respond extremely positively to a research culture that acknowledges

a hierarchy of concern but also finds innovative ways to demonstrate extraordinary compassion for even the least human-like animals. Support for biomedical research will be sustained as a result. Advances in medical research that require invasive animal testing more than ever depend on clear moral justifications, given waning public support for this type of research.²⁶ These six moral principles provide a powerful place to start explaining to ourselves and others what it takes to justify inflicting harm that every reasonable person would prefer to avoid.

Notes

1. C. Darwin, *The Descent of Man and Selection in Relation to Sex* (London: Penguin Classics, 2004).
2. B. Hare, "Survival of the Friendliest: *Homo sapiens* Evolved via Selection for Prosociality," *Annual Review of Psychology* 68 (2017): 155–86.
3. National Research Council, *Guide for the Care and Use of Laboratory Animals* (Washington, DC: National Academies Press, 2010).
4. J. L. McMillan et al., "An International Survey of Approaches to Chair Restraint of Nonhuman Primates," *Comparative Medicine* 67 (2017): 442–51.
5. See position piece: American Association of Universities, "AAU Opposes the Great Ape Protection and Cost Savings Act of 2011" (2012). It was distributed to congressional representatives on behalf of almost all major US research universities and states on page 2, "The Great Ape Protection and Cost Savings Act would halt all research involving chimpanzees, gorillas, orangutans, bonobos and gibbons, including research intended to improve the health of these animals in the wild and captivity" (<https://www.aau.edu/sites/default/files/AAU%20Files/Key%20Issues/Research%20Administration%20%26%20Regulation/AAU-Opposes-Great-Ape-Protection-Cost-Savings-Act.pdf>, accessed 15 October 2018). In contrast see G. Miller, "Sanctuaries Aid Research and Vice Versa," *Science* 317 (2007): 1338–40, which examines how African sanctuaries had already become a major research resource; and B. Hare and S. Yamamoto, *Bonobos: Unique in Mind, Brain, and Behavior* (Oxford: Oxford University Press, 2017), which presents an example of a research program that would have been impossible to conduct within NIH laboratories.

6. See National Research Council, *Chimpanzees in Research: Strategies for Their Ethical Care, Management, and Use* (Washington, DC: National Academies Press, 1997); J. Cohen, "Chimps and Lethal Strain a Bad Mix," *Science* 286 (1999): 1454–55; and J. Cohen, "The Endangered Lab Chimp," *Science* 315 (2007): 450–52.
7. See Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, Institute of Medicine (now Academy of Medicine), *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, DC: National Academies Press, 2011), <https://www.nap.edu/catalog/13257/chimpanzees-in-biomedical-and-behavioral-research-assessing-the-necessity>, accessed 15 October 2018.
8. Committee on the Use of Chimpanzees in Biomedical and Behavioral Research, *Chimpanzees in Biomedical and Behavioral Research*; National Institutes of Health, Office of the Director, "Statement by NIH Director Dr. Francis Collins on the Institute of Medicine Report Addressing the Scientific Need for the Use of Chimpanzees in Research," 15 December 2011, <http://www.nih.gov/news/health/dec2011/od-15.htm>, accessed 15 October 2018; and the follow-up report, Council of Councils, National Institutes of Health, *Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research: Report*, 2013, https://dpcpsi.nih.gov/council/pdf/FNL_Report_WG_Chimpanzees.pdf, accessed 15 October 2018; National Institutes of Health, "Announcement of Agency Decision: Recommendations on the Use of Chimpanzees in NIH-Supported Research," dpcpsi.nih.gov/council/pdf/NIHresponse_to_Council_of_Councils_recommendations_62513.pdf, retrieved 15 October 2018.
9. M. Gruen and B. Hare, "Do Veterinarians or the Public Believe Dog Breeds Differ in Pain Sensitivity?" (manuscript under review).
10. A. Bandura, *Moral Disengagement: How People Do Harm and Live with Themselves* (New York: Worth, 2016).
11. See Hare, "Survival of the Friendliest"; and E. Bruneau et al., "Denying Humanity: The Distinct Neural Correlates of Blatant Dehumanization," *Journal of Experimental Psychology: General* 147 (2018): 1078.
12. See N. Kteily et al., "The Ascent of Man: Theoretical and Empirical Evidence for Blatant Dehumanization," *Journal of Personality and Social Psychology* 109, no. 5 (2015): 901; and N. Haslam and S. Loughnan, "Dehumanization and Infrahumanization," *Annual Review of Psychology* 65 (2014): 399–423.
13. I have conducted noninvasive research in the United States for twenty years. At each university I have worked, I was required to complete online

training. In some way each training program explicitly described non-human primates involved in research as dangerous, violent, or aggressive. None of these programs explained that in their natural habitat primates are not aggressive toward humans or that the species of primates kept in laboratories are in any way unusual compared with other primates in terms of the level of aggression they show in the wild.

14. See T. J. Eddy et al., "Attribution of Cognitive States to Animals: Anthropomorphism in Comparative Perspective," *Journal of Social Issues* 49, no. 1 (1993): 87–101; and J. Vaes et al., "Minimal Humanity Cues Induce Neural Empathic Reactions towards Non-human Entities," *Neuropsychologia* 89 (2016): 132–40.
15. G. J. Mason, "Species Differences in Responses to Captivity: Stress, Welfare and the Comparative Method," *Trends in Ecology & Evolution* 25 (2010): 713–21.
16. See E. L. MacLean et al., "How Does Cognition Evolve? Phylogenetic Comparative Psychology," *Animal Cognition* 15 (2012): 223–38; and A. G. Rosati and B. Hare, "Looking Past the Model Species: Diversity in Gaze-Following Skills Across Primates," *Current Opinion in Neurobiology* 19 (2009): 45–51.
17. See J. Tan et al., "What Influences a Pet Dog's First Impression of a Stranger?" *Learning & Behavior* (2018), <https://doi.org/10.3758/s13420-018-0353-y>; and A. G. Rosati et al., "Assessing the Psychological Health of Captive and Wild Apes: A Response to Ferdowsian et al.," *Journal of Comparative Psychology* 127, no. 3 (2013): 329–36.
18. B. Hare and V. Woods, *The Genius of Dogs* (New York: Oneworld Publications, 2013).
19. G. J. Mason et al., "Frustrations of Fur-Farmed Mink," *Nature* 410 (2001): 35–36.
20. M. J. Prescott and H. M. Buchanan-Smith, *Training Nonhuman Primates Using Positive Reinforcement Techniques: A Special Issue of the Journal of Applied Animal Welfare Science* (New York: Psychology Press, 2016).
21. See M. Bloomsmith et al., "Positive Reinforcement Methods to Train Chimpanzees to Cooperate with Urine Collection," *Journal of the American Association for Laboratory Animal Science* 54 (2015): 66–69; M. L. Graham et al., "Successful Implementation of Cooperative Handling Eliminates the Need for Restraint in a Complex Non-human Primate Disease Model," *Journal of Medical Primatology* 41 (2012): 89–106; K. Westlund, "Training Laboratory Primates: Benefits and Techniques," *Primate Biology* 2 (2015): 119–32; S. Hirata et al., "Brain Response to Affective Pictures in

- the Chimpanzee,” *Scientific Reports* 3 (2013), doi: 10.1038/srep01342; and T. Sakai et al., “Fetal Brain Development in Chimpanzees versus Humans,” *Current Biology* 22 (2012): R791–R792.
22. See L. U. Sneddon et al., “Do Fishes Have Nociceptors? Evidence for the Evolution of a Vertebrate Sensory System,” *Proceedings of the Royal Society of London B: Biological Sciences* 270 (2003): 1115–21; and J. L. McMillan et al., “An International Survey of Approaches to Chair Restraint of Nonhuman Primates,” *Comparative Medicine* 67 (2017): 442–51.
 23. See P. Walsh et al., “Catastrophic Ape Decline in Western Equatorial Africa,” *Nature* 422 (2003): 611; and B. Shapiro, *How to Clone a Mammoth: The Science of De-extinction* (Princeton, NJ: Princeton University Press, 2015).
 24. Bruneau et al., “Denying Humanity.”
 25. Vaes et al., “Minimal Humanity Cues Induce Neural Empathic Reactions towards Non-human Entities.”
 26. D. Grimm, “Opening the Lab Door,” *Science* 360 (2018): 1392–95.

Commentary on the Beauchamp-DeGrazia Framework of Principles

Margaret S. Landi

This commentary is based on my experience working in drug discovery and development, providing veterinary care for laboratory animals, and serving as the chief veterinarian responsible for animal welfare, ethics, and animal research strategy at a large pharmaceutical company and, most recently, my completion of formal education in bioethics. What follows are my thoughts and comments; mine alone.

Many of us in the animal research community face an internal conflict almost every day. We witness firsthand how new treatments are discovered and developed. We recognize that there are new discoveries to be made and that animals remain part of this paradigm. Concomitantly, we see study-based harm to and compromise of the health and well-being of animals in our care. Within our community, any substantive discussions or debates on the ethics of a study design in a protocol occur within an Institutional Animal Care and Use Committee (IACUC). To achieve and document compliance with multiple regulations, guidelines, and institutional policies, IACUCs utilize templates with instructions and questions.¹ Most of the templates request information required by the institution in meeting legal or institutional policies. Prompts to ethical discussion are often limited to details concerning harm–benefit analysis (HBA) and the role of the Three Rs in study design.²

I agree with the premise that HBA and the Three Rs do not provide a robust framework for ethical debate on studies requiring animals. The identification of gaps left by HBA and the Three Rs led Beauchamp and DeGrazia to outline three new pivotal claims. First, “sentient animals have moral status and therefore are not merely tools of research” (p. 2). I believe any sensible members of the animal research or animal protection communities (as defined by the authors) would agree with this statement, though a few might cling to the premise that the only species with moral status is *Homo sapiens*.³

A bit more controversial is the second claim: “the only possible justification for (nontherapeutically) harming animals with moral status, including animal research subjects, is the prospect of substantial and otherwise unattainable social benefits” (p.2).⁴ While benefit is described and justified in all research protocols, it may be hard to show that there is a “prospect of substantial and otherwise unattainable” benefit. One area where this hurdle may be met, and the meeting of it documented, is in vaccine research and development. Vaccination for diseases in which treatment is difficult (e.g., *Bordetella pertussis*) or impossible (e.g., *Herpes zoster*, rabies) can be viewed as achieving “substantial and otherwise unattainable” benefits.⁵ For other treatment modalities and in early discovery work, it is more difficult to assess accurately whether there is a “prospect of substantial and otherwise unattainable” benefits. In practice, however, details on justification and benefit, as submitted by the principal investigator, are often accepted with little or no modification by the IACUC.⁶

Though not discussed in the Beauchamp and DeGrazia principles document, improvement in study design, I suggest, is a way to increase benefit. As is well documented, there is often poor translatability of studies between nonhuman and human animals.⁷ Improvement of study validity by more aggressive questioning of experimental design has the potential to improve benefit in the harm–benefit ratio.⁸

The third and final claim is that “any permissible harming of animals in research is limited by considerations of animal welfare” (p. 3). Harm to an animal is measured by the degree of pain and distress imposed on the animal in captivity and by the study design.⁹ Decisions relating to the extent of harm are based on predictions of compromise of the animal’s welfare. Though the classification of harms may differ between countries, there is broad agreement on three classes of harm: mild (e.g., a simple, noncomplicated needle stick), moderate (e.g., postsurgery pain treated with analgesics), and severe (e.g., clinically evident terminal renal failure).¹⁰ The rodent collagen-induced arthritis model, designed for the study of changes approximating those seen in rheumatoid arthritis, is one example of how discussions of the degree of harm can be linked to animal welfare. During HBA there is in-depth debate on how to reduce harm to animals whose joints will be injured by arthritic changes. Study length, degree of mobility loss, and alternations in behavior are all markers for animal welfare and influence study design.¹¹ Aligned with the three pivotal claims just discussed are what Beauchamp and DeGrazia call the two core values: social benefit and animal welfare.¹² Each core value underlies and supports three principles, and all six principles must be met for a study to be “morally justified by scientific purposes” (pp. 12 and 20). If a study design does not deliver on all six, the study may be scientifically justified but not justified morally.

Before discussing the six principles, I consider it important to comment on the statement that social benefit and animal welfare “are already embraced in animal research regulation, practice, and philosophy even if the implications of these values are not always adequately appreciated in policy and practice” (p. 3). I do not think this is as true as either Beauchamp and DeGrazia or I would like to believe. There are institutions that adhere only to what is written and legally required, thereby creating doubt about the full accuracy of the preceding statement.¹³ Acceptance of the proposed principles, capturing both social benefit and animal welfare, would go a

long way to catalyzing improved practices and debates on animals in research.¹⁴

The first principle under social benefit is one of “no alternative method.” According to this principle, a study should be carried out only if the predicted social benefits are “not ethically obtainable through alternative research methods that do not use live animals” (p. 7).¹⁵ At first this may resonate with “replacement” from the iconic Three Rs, but there is a difference. In a classic Three-Rs conversation, replacement discussions are driven by welfare questions. The “no alternative method” is not based on animal welfare (or science); rather, it asks us to declare that predicted benefits can be feasibly sought only in animal trials. Stated differently, if there is an acceptable or qualified way to get results that does not require animals, even if there is historical precedent for specific models and study paradigms, we must pursue the nonanimal method. I believe most in the animal research community can accept this principle.

When reflecting on Principle 2, “expected net benefit,” those of us in the field must shift away from our present thoughts on harm–benefit analysis and move to risk–benefit analysis, which involves the predicted risks and benefits for humans. (We must also factor in anticipated costs other than risks, but my present point is about risks.) I had some difficulty in understanding this principle. The key for me was to focus on predicted risk and benefit to people and not to confuse this principle with that of predicted harm to animals, which is the third principle under social benefit (the principle of sufficient value to justify harm).

Assessment of Principle 2 requires a discussion of both the predicted benefits and the predicted risks for humans. If the benefits outweigh the risks (and other costs), then the study meets very basic ethical requirements derived from principles. I believe the authors state this principle in order to challenge those involved with science, welfare, study design, and implementation to review past findings and errors and apply what has been learned to improve the expected net benefit of animal studies for humans. Recently several

articles have reviewed nonconcordant data between animals and humans and have identified studies with too small an n to be significant. By reviewing true positives, false positives, false negatives, and true negatives, we can decide, to the best of our ability, if the expected net benefit will be positive for the critical species in this analysis—humans.¹⁶

To meet the third principle, work must be designed so the outcome is one of “sufficient value to justify harm” to the animals. While shadowing the well-established harm–benefit analysis, this principle asks more of us. By accepting the moral status of animals, even on a sliding scale, we have an obligation to debate whether the study is of sufficient value. If it is not accepted that nonhuman animals have moral status, then a study with ill-defined value might still be deemed justified. Examples may be found in lead optimization studies. Often in “lead op,” animals are dosed with new chemical entities. This is early drug discovery work, and it is not unusual for the target of interest to be poorly defined.¹⁷ During IACUC review, the imprecision in lead optimization designs is often accepted after HBA and Three-Rs discussions.

Lead op studies are a part of drug discovery where the largest number of animals, primarily rodents, are used.¹⁸ Change has been difficult due to program milestones, timeline pressures, historical knowledge and precedents, and lack of qualified alternatives. By accepting that animals have some significant level of moral status, this principle obligates researchers to assess and characterize a proposed study (as much as possible) in order to estimate and accept the harms to animals involved in the study.

As a reminder, all three of the principles under consideration (in the framework of six principles) must be fulfilled to satisfy the requirements of moral justification under the principles of social benefit: there is no known acceptable alternative, a prospect of net benefit for humans is defined and analyzed, and the overall study outcome is assessed as having sufficient value when compared with animal harm. These principles are not identical to the Three Rs.

They provide relevant substantive considerations for all who care about animals, and I accept them.

Three additional proposed principles are linked to animal welfare. First is the principle of “no unnecessary harm,” which prohibits harm to or compromise of animal welfare, except where it is necessary for the research. It is important to consider “harm” beyond what is required by the study design. Unnecessary insults to animal welfare may be caused by prolonged transit times, numerous transfer points, and indirect shipping routes. While still not routine, deliberations on moral considerability (or moral status) during IACUC meetings are one way to ensure discussion and debates on the full range of harms that could occur before, during, and after a study.¹⁹

The second principle is one of “basic needs.” Basic needs include, but are not limited to, species-specific housing, food, appropriate handling, and veterinary care. As noted earlier, there are institutions that comply with the law, but this does not always mean the basic needs of a specific species are being met. The most prominent example is related to housing paradigms (e.g., legal size but no allowance for vertical space) of nonhuman primates.²⁰ Some studies require fasting and/or water deprivation, but they are time-bound events and should not result in overall compromise of basic needs. Prospective establishment of endpoints results in reduced severity in many studies, though controversy remains about procedures such as water deprivation of nonhuman primates in neuroscience studies.²¹

The last principle is that “of upper limits to harm.” This principle states that there is a point at which a study should not be approved due to the predicted harm, even if the study exhibits considerable potential for social benefit. Referring to the acceptance of moral status, I agree unambiguously that there should be an upper limit to harm. I state this knowing that studies are required under the Food and Drug Administration’s Animal Efficacy Rule, commonly called the animal rule. Drug

development under the animal rule recognizes that it would be unethical to perform studies with bioterroristic microorganisms in people. Under the animal rule, there are regulations requiring death of controls to ensure the organism being tested is at the correct virulence for the study. For now, I accede to the need for these studies for the following reasons: they cannot be performed ethically in humans; they are based on present therapeutic knowledge; their adverse effects are defined; and there is a specific time limit, though death is an endpoint still required in control animals.²²

Many of us in the animal research community know of the four bioethical principles for human clinical trials: respect for autonomy, nonmaleficence, beneficence, and justice.²³ These principles are not directly applicable to research involving non-human animals where subjects, while having moral status, differ in genus and species and are incapable of verbal communication and consent. In the present framework, Beauchamp and DeGrazia propose six principles, which are linked to the values of social benefit and animal welfare. While I have added some information on batch release and quality-control testing that are important in vaccines, other agents such as biopharmaceuticals with their primate-specific mode of action are not addressed in Beauchamp and DeGrazia's discussion of their six principles. Such additions would make the framework more complete. In my judgment, there also should be more material and deliberation in the text on the topic of basic research.

Still, I believe the six principles must be seriously considered in discussions and debates about the conditions of morally justified animal research, for the following reasons: (1) the principles contain prompts for bioethical questions not recognized or stimulated by HBA and the Three Rs; and, more important, (2) they provide common ground for needed engagement between two communities that in the end both deeply care about animals.

Notes

1. A review of twenty publicly accessible IACUC forms and/or instructions from the twenty top-funded National Institutes of Health institutions revealed that information in four areas was especially frequently requested: (1) details on the staff involved, including training and competency; (2) facts on animals' species, gender, weight, etc.; (3) specific study justification (study "benefit"), including the rationale for involving animals; and (4) harm-benefit and Three-Rs considerations, including level of pain and/or distress (study "harm"). One exemplar is Johns Hopkins University, a top-five-funded university in 2016.
2. Two articles well describe how many view and employ harm-benefit analysis: Aurora Brønstad et al., "Current Concepts of Harm-Benefit Analysis of Animal Experiments—Report from the Aalas-Felasa Working Group on Harm-Benefit Analysis, Part 1," *Laboratory Animals* 50, no. 1, suppl. (2016): 1–20; and Kathy Laber et al., "Recommendations for Addressing Harm-Benefit Analysis and Implementation in Ethical Evaluation - Report from the Aalas-Felasa Working Group on Harm-Benefit Analysis, Part 2," *Laboratory Animals* 50, no. 1, suppl. (2016): 21–42.
3. As reviewed by Beauchamp and DeGrazia, the body of knowledge on sentience and moral status increases every day. Many people now believe animals have moral status, though status that is not equal to that of humans. It is important to note that some accept the traditional Judeo-Christian notion that humans have a special place in creation, translating to the belief that only humans have moral status. For further information, see Mark Rowlands, *Can Animals Be Moral?* (New York: Oxford University Press, 2015).
4. As I discuss in the text, accurate prediction of benefit is difficult; a scientifically sound hypothesis may not always translate into new or improved treatments and therapies. Authors from Switzerland and Austria state that "whether potential prospective societal benefits are realized is (a) impossible to predict and (b) exceeds the scope and responsibility of researchers." Also part of their argument is that "the emphasis on practical benefits has the drawback of driving researchers into speculation on the practical benefit of their research and, therefore, into promising too much. Repeated failure to deliver proclaimed practical benefits will lead to a loss of trust and credibility in research." Herwig Grimm et al., "The Road to Hell Is Paved with Good Intentions: Why Harm-Benefit Analysis and

Its Emphasis on Practical Benefit Jeopardizes the Credibility of Research,” *Animals* 7, no. 9 (2017): 1–6; final quote on 1.

5. Many vaccines still require animals, either in quality control tests or in batch release assays. See Marieke Hoonakker, Juan Arciniega, and Coenraad Hendriksen, “Safety Testing of Acellular Pertussis Vaccines: Use of Animals and 3Rs Alternatives,” *Human Vaccines & Immunotherapeutics* 13, no. 11 (2017): 2522–30.
6. Benefit is often predicted on the basis of literature review, institutional references, and the experience of scientists. A decision can be made with this information in an objective manner but is nonetheless somewhat subjective. Subjectivity arises when unrecognized bias limits the references that are reviewed and how decisions are made. Refer to Isabella W. Y. Mak, Nathan Evaniew, and Michelle Ghert, “Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment,” *American Journal of Translational Research* 6, no. 2 (2014): 114–18; and Catherine A. Schuppli, “Decisions About the Use of Animals in Research: Ethical Reflection by Animal Ethics Committee Members,” *Anthrozoös* 24, no. 4 (2011): 409–25.
7. More and more literature points to the unreliability of some animal work due to the lack of translatability and/or reproducibility of published results. However, this emerging information should not be interpreted as “all animal studies are doomed to failure.” Note the following references: Lucile Vogt et al., “Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor,” *PLOS Biology* 14, no. 12 (2016): 1–24; Emma Yasinski, “Study Questions Animal Efficacy Data Behind Trials,” *Science* 360, no. 6385 (13 April 2018): 142; Thomas S. Reichlin, Lucile Vogt, and Hanno Würbel, “The Researchers’ View of Scientific Rigor: Survey on the Conduct and Reporting of in Vivo Research,” *PLOS ONE* 11, no. 12 (2016): 1–20; Vogt et al, “Authorization of Animal Experiments”; and Hanno Würbel, “More than 3Rs: The Importance of Scientific Validity for Harm-Benefit Analysis of Animal Research,” *Laboratory Animals* 46, no. 4 (2017): 164–66.
8. Increasing validity is one tool for enhancing the strength of study design and its translatability—which in turn increases benefit. See Kathryn Bayne and Hanno Würbel, “The Impact of Environmental Enrichment on the Outcome Variability and Scientific Validity of Laboratory Animal Studies,” *Revue scientifique et technique—Office international des épizooties* 33, no. 1 (2014): 273–80; and Würbel, “More than 3Rs.”
9. You will notice that I do not use the word “suffering” in my commentary. Suffering is referred to in British law and the EU directive, based on Jeremy

Bentham's famous quote: "The question is not, Can they *reason*? nor, Can they *talk*? but, Can they *suffer*?" Jeremy Bentham, *An Introduction to the Principles of Morals and Legislation*, in J. H. Burns and H. L. A. Hart (eds.), *The Collected Works of Jeremy Bentham* (Oxford: Oxford University Press, 1996), 283. While animals do demonstrate compassion for others and grief at a loss, for me suffering has a mental stress component, which lasts over time and is often triggered by event anniversaries. Grief shown by a mare on the death of her foal is visible, vocal, and lasts for several hours to days. However, there is no display of grief or loss one year after the death of the foal.

10. The categories of the US Department of Agriculture differ from UK and EU definitions, but they are all tied to the degree of harm inflicted on the animal by the experiment. The United States does not use the terms "minor," "moderate," and "severe" in its law. See United States Department of Agriculture, Animal and Plant Health Inspection Service, "Research Facility Annual Summary Report," https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_obtain_research_facility_annual_report, retrieved 5 July 2018.
11. Rodent models of rheumatoid arthritis, specifically the collagen-induced arthritis model, are exemplars of a model in which animals are subjected to pain. See Penny Hawkins et al., "Applying Refinement to the Use of Mice and Rats in Rheumatoid Arthritis Research," *Inflammopharmacology* 23, no. 4 (2015): 131–50.
12. "Social benefit" was not a term I was familiar with in the context of animal research. Some research and discussion with Beauchamp and DeGrazia led me to realize that the "benefit" in "social benefit" is not to the animal subjects or to the animal species (except in veterinary research), but rather to humans. The authors are referring to benefit to society. One reference of interest in the area of human research subjects is David B. Resnik, "Examining the Social Benefits Principle in Research with Human Participants," *Health Care Analysis* 26, no. 1 (2018): 66–80.
13. As an example, the law will refer to provisions for the psychological well-being of nonhuman primates. Many consortia and professional groups have peer-reviewed and published articles on improving housing and care to supplement legal guidance. See Kate C. Baker et al., "Comparing Options for Pair Housing Rhesus Macaques Using Behavioral Welfare Measures," *American Journal of Primatology* 76, no. 1 (2014): 30–42; Jim Weed et al., "The Behavioral Management Consortium: A Partnership for Promoting Consensus and Best Practices," in *Handbook of Primate*

Behavioral Management (Boca Raton, FL: CRC Press, 2017), 9–24; and Jessica Crast, Mollie A. Bloomsmith, and Trina Jonesteller, “Effects of Changing Housing Conditions on Mangabey Behavior (*Cercocebus atys*): Spatial Density, Housing Quality, and Novelty Effects,” *American Journal of Primatology* 77, no. 9 (2015): 1001–14. .

14. Many contract research organizations (CROs) state clearly a commitment to high standards. Covance, Charles River Laboratories, and Envigo—the big three CROs in North America, Europe, and Asia—are examples. However, there are differences in housing at even large CROs depending on the country requirement, unless specific caging paradigms are requested by their clients. It should be noted that the country laws are always met, and most animal care and use programs are accredited by AAALAC International, which uses three primary standards in the accreditation process. They are outlined in the 8th edition of National Research Council, *Guide for the Care and Use of Laboratory Animals* (Washington, DC: National Academies Press, 2011); *Guide for the Care and Use of Agricultural Animals in Research and Teaching* (FASS 2010); and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Council of Europe (ETS 123).
15. Some of the wording is similar to that in the well-known chimpanzee report of the Institute of Medicine’s Committee on Assessing Necessity of Chimpanzees in Biomedical and Behavioral Research of the National Research Council, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (Washington, DC: National Academies Press, 2011).
16. Refer to the following for more details: David DeGrazia and Jeff Sebo, “Necessary Conditions for Morally Responsible Animal Research,” *Cambridge Quarterly of Healthcare Ethics* 24, no. 4 (2015): 420–30; Aysha Akhtar, “The Flaws and Human Harms of Animal Experimentation,” *Cambridge Quarterly of Healthcare Ethics* 24, no. 4 (2015): 407–19; and Matthew Clark and Thomas Steger-Hartmann, “A Big Data Approach to the Concordance of the Toxicity of Pharmaceuticals in Animals and Humans,” *Regulatory Toxicology and Pharmacology* 96 (2018): 94–105.
17. Lead optimization is part of the drug discovery phase when lead compounds are synthesized. According to Wikipedia, “[N]ew analogs with improved potency, reduced off-target activities, and physiochemical/metabolic properties suggestive of reasonable (emphasis added) in vivo pharmacokinetics. This optimization is accomplished through

chemical modification of the hit structure, with modifications chosen by employing knowledge of the structure–activity relationship (SAR) as well as structure-based design if structural information about the target is available. Lead optimization is concerned with experimental testing and confirmation of the compound based on *animal efficacy models* (emphasis added) and ADMET (in vitro and in situ) tools. That may be followed by target identification and target validation.” For an overview of lead optimization I refer the reader to “Hit to Lead,” https://en.wikipedia.org/wiki/Hit_to_lead, retrieved 24 January 2018.

18. For those who would like to learn more about drug discovery and development, here are two excellent references: Konrad H. Bleicher et al., “A Guide to Drug Discovery: Hit and Lead Generation—Beyond High-Throughput Screening,” *Nature Reviews Drug Discovery* 2, no. 5 (2003): 369–78; and C. W. Lindsley et. al, “Lead Optimization in Drug Discovery,” in Natanya Civjan (ed.), *Chemical Biology: Approaches to Drug Discovery and Development to Targeting Disease* (New York: Wiley, 2012), 65–81.
19. Moral considerability, an animal’s telos, and other concepts have been discussed as useful for improving ethical debate in IACUC meetings or other fora. See Margaret S. Landi, Adam J. Shriver, and Anne Mueller, “Consideration and Checkboxes: Incorporating Ethics and Science into the 3Rs,” *Journal of the American Association for Laboratory Animal Science* 54, no. 2 (2015): 1–7; and Bernard E. Rollin, “Telos, Conservation of Welfare, and Ethical Issues in Genetic Engineering of Animals,” in *Ethical Issues in Behavioral Neuroscience* (New York: Springer, 2014), 99–116.
20. See note 13.
21. The majority of institutions, via policy, standard operating procedures, and/or practices or procedures, define their understanding of basic needs or core principles. Most experiments have specific endpoints in place, prior to the start of the study. See P. Hawkins et al., “A Guide to Defining and Implementing Protocols for the Welfare Assessment of Laboratory Animals: Eleventh Report of the Bvaawf/Frame/Rspca/Ufaw Joint Working Group on Refinement,” *Laboratory Animals* 45, no. 1 (2011): 1–13. Study designs that may “deny basic needs,” for example withholding food or water, must have timelines in place to prevent starvation or dehydration. See National Research Council, *International Animal Research Regulations: Impact on Neuroscience Research—Workshop Summary* (Washington, DC: National Academies Press, 2012), 1–89, esp. 61. See also Mark J. Prescott et al., “Refinement of the Use of Food and Fluid Control as Motivational Tools for Macaques Used in Behavioural

Neuroscience Research: Report of a Working Group of the NC3Rs,” *Journal of Neuroscience Methods* 193, no. 2 (2010): 167–88.

22. This may seem to imply that I do not agree with an upper limit of harm, but I do. Ethical questions of the animal rule are well laid out in Anne Barnhill, Steven Joffe, and Franklin G. Miller, “The Ethics of Infection Challenges in Primates,” *Hastings Center Report* 46, no. 4 (2016): 20–26. And new challenges are always emerging, requiring debate and decision. See Elaine Haddock et al., “A *Cynomolgus macaque* Model for Crimean–Congo Haemorrhagic Fever,” *Nature Microbiology* 3, no. 5 (2018): 558, <https://www.nih.gov/news-events/news-releases/nih-scientists-develop-macaque-model-study-crimean-congo-hemorrhagic-fever>, retrieved 29 April 2018; Food and Drug Administration, “Product Development under the Animal Rule,” 1–54, <https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf>, retrieved 14 May 2018; and “Animal Efficacy Rule,” *Wikipedia*, https://en.wikipedia.org/wiki/Animal_efficacy_rule, retrieved 23 June 2018.
23. This framework for biomedical ethics was developed by Tom L. Beauchamp and James F. Childress in *Principles of Biomedical Ethics*, now in its 8th edition (New York: Oxford University Press, 2019).

The Six Principles, Philosophy, and Applying Human Ethics to Animals

Julian Savulescu

The Six Principles

The six principles of Beauchamp and DeGrazia (BD) are arguably the most constructive step forward in the ethics of animal experimentation in the past fifty years. BD aim to develop and significantly augment Russell and Burch's principles of humane experimental technique, which involved the so-called Three Rs: replacing sentient animals with other models where possible; reducing the number of animal subjects to what is needed for statistical adequacy; and refining techniques to reduce animal suffering. BD's reason for moving beyond the Three Rs is that "this framework does not feature general moral principles that display the core values at work in animal research ethics. In addition, the Three-Rs framework does not adequately address the costs and benefits of animal research to human beings or include a comprehensive program of animal-subjects protection" (p. 7).

I want to further these aims of the six principles. BD correctly observe that "the core values of animal research ethics are *social benefit* and *animal welfare*" (p. 3). The critical issue is how to weigh human interests against animal interests. This is, in practice, where a great fudge can loom large: either the human benefit is overestimated or the harm to animals is underestimated. I want

to address how these benefits and harms can be more precisely evaluated and how they should be balanced.

In this first section, I aim to explicate further Principle 5 (the principle of basic needs). In later sections (“Mindless and Radically Genetically Modified Animals. . .” and “Minimal Beneficence. . .”), I will explicate Principle 6 (the principle of upper limits to harm) and Principle 3 (the principle of sufficient value to justify harm). Basic needs will be especially prominent in my discussions. However, my points are often sufficiently general that they pertain to all of the six principles: there are value judgments in interpreting and specifying all these principles. We need new ways to think about fleshing them out. The most innocuous of the principles are 1 (the principle of no alternative method) and 4 (the principle of no unnecessary harm), but even in these cases, we will need to specify what counts as “alternative” and “unnecessary.” There might be some alternative method, but it might be difficult to implement. There might be some way of avoiding pain, but it might be wasteful of resources and have significant opportunity costs. What is really meant is “no reasonable alternative,” and we then need a way of deciding what is reasonable, in which case we are back to weighing human and animal interests.

This problem does not escape BD. It is clearly expressed when they write, “*The Principle of Basic Needs* requires investigators and caretakers to meet animal subjects’ basic needs *unless failure to meet one or more basic needs is an unavoidable consequence of, and morally justified by,* scientific procedures in a well-designed protocol that satisfies the three principles of social benefit” (p. 14, emphasis added). One example of successful specification or “precisification” is BD’s list of basic needs. This list makes clear what must be addressed by researchers and ethics committees. It supplies a plausible catalog of the basic needs:

- Nutritious food and clean water
- Safe shelter

- Adequate stimulation, exercise, and opportunities for species-typical functioning
- Sufficient rest to maintain physical and (where applicable) mental health
- Veterinary care
- For social species, access to compatible conspecifics or social group members
- Freedom from significant experiential harms such as pain, distress, and suffering
- Freedom from disease, injury, and disability
- Freedom of movement with adequate space

It is controversial whether the following is a basic need:

- Freedom from premature death (p. 15).

My procedure hereafter will be as follows: after commenting on the evolution of research ethics from a “big picture” perspective, I will address the issue of the badness of premature death in animals. I will then try to show both how these animals’ interests in avoiding premature death can be weighed against human interests and how we can set an upper limit to harm (following Principle 6). These matters are critical to questions of the practicability of the BD principles. Since BD do not specifically consider novel animals who have different needs—those who have been created by new reproductive technologies or by gene editing to have different needs—I will also address the ethics of creating such animals, including animals who do not feel pain or suffer.

In what follows, I will use two well-developed theoretical ideas from human ethics and apply them to animal ethics:

1. The veil of ignorance. This procedure was developed by John Rawls to identify what would constitute a just and fair state of affairs for humans. It involves imagining oneself behind a veil or curtain, not knowing who in society one would be,

whether one would be the best off, the average person, or the worst off. Rawls famously claimed that from behind the veil, one would choose the social and legal arrangements that made the worst off as well off as possible (maximin).¹

2. The distinction between two different kinds of reasons: person-affecting and impersonal reasons. Person-affecting reasons involve harm or benefit to particular human beings, while impersonal reasons involve making the world more generally better or worse, without there being harm or benefit to any particular individual.²

I will support the idea that ethics, including ethical judgments that start from human ethics but also apply to animals, is universalizable.

Big Picture: The Evolution of Research Ethics

As BD briefly observe, the *Belmont Report* was a major advance in the ethical oversight of human research. Beauchamp was a driver of that report. It was and remains a great achievement that was published by the National Commission for the Protection of Human Subjects at a particularly timely point (1978) in the early history of bioethics. In this report (as elsewhere in bioethics), human ethics committees, or institutional review boards (IRBs) as they are called in the United States, were given responsibility for ethical oversight of research involving humans and were situated at the center of the process of approving research protocols. Today IRBs flourish and tightly control research throughout the world. However, it is time to reinvent ethics review to address the ways technology, ethics, and science have evolved. As I have argued elsewhere, ethics committees now often obstruct valid research, with

lethal consequences,³ and often fail to properly execute their ethical obligations.⁴

We now need a second revolution in both human research ethics and animal research ethics. I have argued that the key element of human ethics is ensuring that the risks involved in research are “reasonable” rather than minimal. The five criteria I have outlined for reasonable risk in humans are remarkably similar to those BD outline for animals. In determining whether the risks of participation in research are reasonable, the following factors are relevant:⁵

1. Is there a known risk to participants prior to the commencement of the study, and what is its magnitude, based on evidence available at the time?
2. Should any nonhuman or epidemiological research, systematic overview, or computer modeling be performed prior to the study to better estimate the risk to participants or obviate the need for the use of human participants?
3. Could the risk have been reduced in any other way? Is it as small as possible?
4. Are the potential benefits of this study (in terms of knowledge, improvement of welfare of trial participants or other people) worth the risks?
5. Could this research generate knowledge that is likely to significantly harm either participants or others outside the research, now or in the future?

The same kinds of consideration can and should be applied to animal research ethics by substituting “animal” for “human”: What is a reasonable risk to the animal subject or a reasonable harm and what is proper oversight of levels of risk?

In ethics, people often think in polar terms such as safe versus unsafe, proven versus unproven, and certain versus uncertain, but

much of ethics is gray. Things are rarely entirely necessary or safe. There are costs and benefits as well as probabilities, and these have to be weighed across different populations, such as current patients versus future patients⁶ and animals versus humans. We need new ways to think more robustly and deeply about these inescapably ethical and philosophical questions of fairness and justice, and BD do a great job of delineating the arena. These are not mere scientific questions; they are fundamental moral questions.

BD point to the central role of animal research ethics committees. These are important, but they must evolve too and increase the professionalism and sophistication of their deliberations. I have argued elsewhere that their judgments should be objective, not merely subjective.⁷ The current major problem is that committee members have wide discretion to decide cases on their intuitions, including those about whether or not there is “sufficient scientific justification” or “sufficient protection of animal welfare.” We should do better than that. We need principled ways of thinking about the six principles and instantiating them in practice. This commentary is an attempt to think about this problem.

The Reincarnation Test

Imagine that Indian religions—Buddhism, Hinduism, and Jainism—are right. Reincarnation exists. After death, your spirit enters the ether. In this world of reincarnation, you could come back in the next life either as a different human being or as an animal (“animal” is shorthand for “nonhuman animal” in this commentary). What system of animal ethics would you choose? The reincarnation test is a version of the veil of ignorance. Addressing this question through a thought experiment about reincarnation can help one achieve an impartial view of human uses of animals in research. I would balance the benefits of the use of animals in research now against the life I might lead as a rat, monkey, or other laboratory animal.

Animal research might lead to medical breakthroughs that prolong my life or improve its quality now or in the future as a human. But it also might not, and in the reincarnation model I might come back as a monkey subjected to painful procedures, kept in a cage, with a much shortened life.

From this position behind the veil of ignorance,⁸ I would choose the various protections afforded by the six principles that BD have developed. I would want there to be a reasonable chance the research would lead to human benefit, and I would want animals to have a reasonably decent life. I want, however, to suggest a benchmark for what a reasonably decent life is for an animal, one that I believe is entirely consistent with the BD account. I want to do so using the reincarnation thought experiment and the philosophical model of a veil of ignorance, for at least three reasons:

1. While some philosophers argue that animal suffering counts the same as human suffering,⁹ others argue that animal suffering counts for less than human suffering.¹⁰ Even if the latter is true, there are vastly more animals than humans. There are 7 billion humans. While there are fewer than 800 million vertebrate lab animals, there are more than 24 billion vertebrate farm animals,¹¹ a figure that does not include pets. The chances of coming back as an animal directly under human control are vastly greater than the chances of benefiting significantly in our lives from animal research or coming back as a human. If one considers all of the future and if current trends continue, the sheer number of future animals under human control will be vast.
2. There is no good reason to apply different standards to research than to other areas of life. The ethics we derive for animals should apply not only to research, but to farming and the rearing of pets—a point about consistency in our thinking about animal ethics generally. The same basic standards of

protection should apply to all animals whose lives are directly and intentionally controlled by humans.

3. Aristotle's principle of equality appropriately requires that we treat like cases alike unless there is a morally relevant difference.

I will now assume that these three reasons and the veil of ignorance idea are acceptable and will move on to examine whether the principles that should govern imposing harm or risk of harm on humans for public interest or social reasons can be extended to animals.

The Veil of Ignorance, Lethal Experimentation, and an Uncontrollable Epidemic

To take more seriously how we should treat animals, we should start with how we should treat humans. In the bioethics community we have thought far more about human ethics than about animal ethics, so we should try to learn how to generalize from human ethics to animal research ethics. While all guidelines for medical research proscribe significant harm to humans, there are good reasons to question the ethical applicability of such proscriptions in all cases. Before considering research ethics, I find it helpful to consider the conditions under which intentionally killing human beings in an extreme emergency might be morally justified.

Imagine that an uncontrollable epidemic afflicts humanity. The disease is highly contagious, and eventually every single human will be affected. Those afflicted fall unconscious. Five out of six people never recover and die within days. One in six people mount an effective immune response. They recover over several days and lead normal lives. Doctors can test people on the second day, while they are still unconscious, and determine whether they have

mounted an effective antibody response or whether they are destined to die. There is only one treatment. Doctors can extract all the blood from the one in six people who do mount an effective antibody response on day 2, while they are still unconscious, and extract the antibodies. There will be enough antibodies to save five of those who don't mount responses, though the extraction procedure will kill the donor. The five will go on to lead normal lives, and the antibody protection will cover them for life.

If you were a person in this uncontrollable epidemic, which policy would you vote for? The first policy, inaction, is one in which nothing is done. One person in six of the world's population will survive. The second policy is extraction, which kills one but saves five others. There is no way to predict who will be an antibody producer. You don't know if you will be one of the six who can mount an immune reaction or one of the five in six who won't manage to mount an immune response and will die without the antibody serum.

Put simply, you don't know whether you will be one who would survive or one who would die without treatment. All you know for certain is that you will catch the disease and fall unconscious. You may recover or you may die while unconscious. Inaction gives you a 1 in 6 chance of being a survivor. Extraction gives you a 5 in 6 chance.

This case is easy for many consequentialists. Extraction saves five times as many lives and should be adopted because it has the best overall consequences. But which would you choose behind the Rawlsian veil of ignorance, not knowing whether you would be immunocompetent or immunodeficient? I would choose extraction. I would definitely become unconscious, like others, and then there would be a 5 in 6 chance of waking up to a normal life. This policy could also be endorsed on Kantian contractualist grounds. Not only would rational self-interest behind a veil of ignorance endorse it, but it could be willed as a universal law. Consequentialism and contractualism here converge.¹² I believe other moral theories would also endorse extraction.

While in an uncontrollable epidemic we can consent in principle to the possibility of being killed, animals typically cannot consent to research performed upon them. However, if we imagine the lives of the noncompetent animals and humans affected by a decision, the veil of ignorance provides a kind of rational impartial consent. For example, we could imagine what it would be like to be unconscious (nothing) and form a view about the interests of such an individual receiving life-sustaining medical treatment.

Extending the Argument to Animals: A Fair Go for Animals

The reasoning in the preceding section can be extended to both lethal experimentation and nonlethal but harmful experimentation on animals. Return to reincarnation. What kind of animal life would we choose if we might be either a human or a lab animal? First, basic needs would have to be met, thereby satisfying the BD principle of basic needs. What we might want is something like a “fair innings” or “fair go”¹³ approach for the affected animals. This would be a life that not merely avoided negatives—freedom from pain, hunger, and the like. It would have to have positive features as well:

- socialization
- play
- instinctive behavior
- procreation and offspring rearing
- happiness, contentment

BD cover important headings of this sort in their list of basic needs, but we need more detail on what such a life would be like. For example, if I were to return as a chicken, I would minimally want the following:

1. A suitable social environment (no more than a few hundred conspecifics).
2. An ability to consume and forage for various types of food (not just a standard mash diet).
3. An ability to express the full variety of natural behaviors: dust-bathe in suitable substrate (soil, fresh litter, or sand; not in manure/litter mixtures); sunbathe (UV lamps or sun); perch; lay eggs in a secluded nest; forage; and so on.
4. Appropriate housing to provide ambient temperatures and shelter from predators.
5. Being killed painlessly before becoming seriously sick or injured.¹⁴

Let's assume this chicken is in all morally relevant respects similar to research animals with comparable moral status. How long should such a research animal live? Here we can employ the reincarnation test. How long would we want to live as a research animal if we did not know whether we would be reborn as a human who might benefit from research or as an animal whose life would be shortened? What I would want as a chicken is a decent life. A decent minimum for a chicken (or "fair innings," as it has been termed in human ethics—sometimes taken to be "three score and ten") might be to reach sexual maturity. By engaging in sexual behavior and procreating, such an animal would have achieved a major important life "milestone" for the species.

The degree of self-consciousness of animals also matters. The more self-conscious the animal, the more a longer life presumably matters because the animal has expectations, perhaps even plans, for the future. The more complex and rich one's mental life, hopes, dreams, expectations, and memories, the more tragic it would be for that life to be cut short.¹⁵

If an animal lacks self-consciousness, less is lost in premature death. While it might be a decent life for a chicken to live long enough to reach, say, sexual maturity, if chickens lack significant

self-consciousness, then it might not be seriously wrong to end the chicken's life before that point for some especially important scientific research, though it may not be justifiable for the production of food. Thus we might believe that the criteria just listed ought to be met while a chicken is alive, but it could be ethical to kill it painlessly before that point for some pressing need. However, it would be wrong to shorten the life of a great ape before the decent minimum because an ape, unlike a chicken, is significantly self-conscious, so the loss imposed on the ape would be greater than that imposed on the chicken.

For purposes of animal research ethics, it seems reasonable to assume that if we bring a sentient being into existence to be a research subject, we should do so only if we can give it a minimally decent life while it is alive, and self-conscious animals should have a fair set of innings. For example, if one chooses to have a pet, that pet should have a minimally decent life as judged by the principle of basic needs. It need not have the very best chance of the best life. A sufficiently good life is enough.

Mindless and Radically Genetically Modified Animals: Person-Affecting versus Impersonal Reasons

In this section, I will give a philosophical explication of BD's final principle: the principle of upper limits to harm. This somewhat different subject concerning research with animals is about radical genetic modification, such as creating animals without minds. In "The Moral Status of the Cloning of Humans,"¹⁶ Michael Tooley raised the possibility of creating cloned anencephalic human infants as a source of organs for transplantation. This approach is extendable to research. Gene editing of gametes or embryos could be used to create mindless anencephalic human infants who could

be used for experimentation, perhaps sparing animals who can experience pain from experimentation.

Similar proposals have been made to create animals that do not feel pain, as a way of reducing suffering.¹⁷ In part, breeding has already achieved modifications of this kind: some chickens have been bred to not care about their eggs.¹⁸ In order to ethically evaluate such proposals for creating modified animals for research, we can employ a distinction drawn by Derek Parfit in human ethics between modifications that are identity-altering (that is, they affect which or whether an individual comes into existence) and modifications that are identity-preserving (that is, they affect an already existing individual for better or worse). To return to the human example, gene-editing an embryo to be deaf would be like deafening a future child, say by cutting its auditory nerves. This would be person-affecting (and therefore identity-preserving) and so more wrong than selecting a human embryo that was created from eggs or sperm with an already existing and unavoidable mutation for deafness. This might be impersonally wrong, but less wrong than causing person-affecting harm.¹⁹ In general, many philosophers hold that person-affecting wrongs are worse than impersonal wrongs.²⁰

Similarly, genetically altering an already existing animal not to care about its young or not to feel pain is identity-preserving, harmful, and *prima facie* wrong. (I am here assuming an animal incapable of experiencing pain will overall lead a worse life, for example, by injuring itself or by facilitating more crowded confinement.) It is wrong to gene-edit animals so that they suffer from disease—unless we follow the qualifications in BD's moral framework that allow certain harms to research animals when necessary for and morally justified by scientific purposes. Thereby the reason for the wrongness of gene editing to make an animal's life worse might be outweighed by reasons of scientific and human benefit.

We might think that using animals having characteristics that are inextricably tied to their identity and lower their quality of life

is not wrong. For example, it seems that using an animal that could not otherwise exist except for some genetic disposition that lowers its quality of life but makes it more useful to humans is not wrong. A mule is bred (by mixing donkey sperm and a horse egg) to work hard, so imposing hard work on it might not be thought wrong. However, this assessment would be a mistake. Even if it is a greater wrong to deafen a human embryo than it is to select a naturally deaf embryo, it would be wrong not to gene-edit or otherwise correct deafness in a naturally deaf embryo. Indeed, I believe it would be as wrong as it is to deafen an embryo. So too the amount of work a mule should be subjected to is governed by the six principles, not by the fact it was bred to work hard. When we have the power to improve human lives, there are strong reasons of beneficence for improving them and of nonmaleficence for not harming them. And so too for animals. If we could gene-edit out the tendency of hens bred not to care about their own eggs, we should do so if it would make their lives better (other things being equal).

The impersonal versus animal-affecting distinction does not allow us to create or use animals with lower prospects of well-being when we can use technology like gene editing to improve their lives. Creating animals to not feel pain or even using naturally occurring breeds (where this feature could be corrected) would not get us off the hook. Our obligations to animals stand.

Suppose a genetic modification would alter identity. For example, genetically modifying an embryo so that the animal would never be conscious would be identity-altering (on some accounts of personal identity—given the assumption, which I find plausible, that the capacity for consciousness creates a new individual with a mind). This modification would be akin to preventing the animal with consciousness from coming into existence. It would be like abortion or embryo destruction. This would not be wrong assuming abortion or embryo destruction is permissible. Creating such a mindless animal would be like creating *in vitro* meat for human consumption.²¹

To summarize thus far, while it would be wrong to modify animals who can or would experience pain to not experience pain, it would not be wrong to create unconscious animals from scratch. And it may not be necessary to go all the way to unconsciousness. For example, gene-editing a pig embryo (before the animal comes into existence with interests) so that the resulting animal was so severely retarded that it had few interests would be morally akin to destroying the pig embryo and would be identity-altering. In such cases, one is not harming the animal (for example, the pig) by lowering its capacity to experience pain. One is stopping the pig from coming into existence and replacing it with a different, severely retarded individual animal.

Such an account can be applied to non-self-conscious animals once they exist, for example chickens. To painlessly kill a chicken is permissible because it lacks a higher-order mental property such as self-consciousness. If an animal has mental states but minimal psychological continuity and connectedness—minimal self-awareness over time—then biological modification of the chicken to remove its consciousness is not wrong; it is akin to killing it. And this extends to other radical modifications that fracture the chain of identity. It is like creating a new animal. So, paradoxically, while it is wrong to lower a chicken's capacity to experience pain (because it is harmful in the "chicken"-affecting sense), it may be a lesser wrong to make that chicken unconscious or severely retarded. However, there may be impersonal reasons not to create such animals (for example, it would be better for the world if there were happy chickens rather than mindless chickens, even if it would not be better for any individual chicken).

To summarize this section, lowering the capacities for a good life in animals who do already or will exist (either through genetic selection or editing) is *prima facie* wrong and violates the principle of upper limits to harm by causing significant harm. However, certain modifications would not cross the threshold of this principle. Radically modifying the early stages of life

of a self-conscious animal prior to that animal's achieving self-consciousness is not wrong on grounds of nonmaleficence if it is identity-altering, though it may be wrong on other impersonal grounds. Similarly, gene editing or other biological modification of characteristics of non-self-conscious animals is not wrong on animal-affecting grounds of harm if it is identity-altering (for example, by removing consciousness or creating severe cognitive impairment), though it may be wrong on other impersonal grounds.

Minimal Beneficence or a Duty of Easy Rescue

According to minimal beneficence or a duty of easy rescue, where risks of performing an action are minimal to small for the rescuers and the benefit (or harm averted) to others is large, we should perform that action. Thus when the benefit to animals of some act (such as supporting humane farming) is great, we should act in that way if the cost to humans is sufficiently small. The reverse is also true: perhaps we should live slightly shorter lives so that our research animals will have much better lives, in accordance with fair innings arguments. Such considerations also imply that animal research serving as preliminary studies for pediatric research might be more justifiable than research into chronic conditions that affect people after their own fair innings.

The principle of minimal beneficence is consistent with several of BD's six principles:

The Principle of Sufficient Value to Justify Harm. This principle will not be met if the benefit to humans is very small and the harm to animals large.

The Principle of Basic Needs. This principle will generally entail that harm to the animal is great if basic needs are not met.

The Principle of Upper Limits to Harm. This principle identifies the point at which harm to the animal is great.

Few would deny minimal beneficence or a duty of easy rescue. This moral norm clearly converges with at least three of the six principles.

Conclusion

In the context of scientific research we may have good reasons for bringing animals into existence as research subjects, especially when they are to be given high-quality lives as judged by the BD principle of basic needs. However, these reasons may be outweighed by animal-affecting considerations, and in practice we may have only weak reasons, if any, for bringing animals into existence for their own sake. If we do bring animals into existence, strong animal-affecting reasons require us to ensure that these animals have a high probability of a sufficiently good life, although these reasons must be weighed in the context of scientific research against human-centered reasons. The facts may be such that some decrement in the *length* or the *quality* of the animal's life is justified for research on the basis of the BD principles of social benefit (assuming the BD principles of animal welfare are also satisfied), just as a decrement in a human being's length or quality of life could be justified in a context of research on human subjects by similar reasoning.²²

Our attitudes toward and practices involving animals are often wildly parochial and inconsistent. It is instructive to compare the enormous lengths to which people go to provide for their pets (even bequeathing them their entire fortune)²³ with the treatment of lab animals all the way to factory farming, where little real consideration of animal welfare occurs. In an incident that caused an uproar in the United States, a science teacher fed a dying puppy to a pet tortoise in front of pupils (and faced six months in jail for

doing so).²⁴ Officials killed the tortoise. In Japan, dogs and cats enjoy special legal protections. Koreans have been denounced for farming and eating dogs, while we happily eat pigs. Some species of fish are protected, like the shark (which kills many fish), but not others. Our treatment of animals seems largely driven by whether we see them as friendly, attractive, or special or useful to us. These drivers are understandable, but they do not provide moral justifications of our preferences in animal research ethics.

In my arguments I have tried to show that BD are right to consider principles as basic to justification. BD have taken animal ethics to the next level and have given reasons why it is now time to further explicate and specify their six principles as operationalizable criteria for animal research—and for human–animal relations more generally. I have tried to show how philosophical approaches to dilemmas in human ethics—the veil of ignorance and the distinction between person-affecting and impersonal reasons—can help us to more precisely operationalize the six principles. Animal ethics is as complex and difficult as human ethics, though we don’t yet realize it.

Around forty years ago Tom Beauchamp and James Childress revolutionized medical ethics by introducing the four principles of biomedical ethics²⁵—respect for autonomy, beneficence, nonmaleficence, and justice. These were intended to be “midlevel” principles between a variety of ethical theories and approaches and actual medical practice. In twenty-five years of practice as an academic practical ethicist, I have found these principles invaluable. However, they leave much open for rich ethical discourse: What is autonomy, how much beneficence is morally required (for example, is it merely a duty of easy rescue or a much stronger duty), and what constitutes justice? In the same way, the six principles of Beauchamp and DeGrazia as set forth in this volume are best interpreted as the animal research equivalent: midlevel principles that leave open for many decades to come a rich body of insights that can and should inform our interpretative and elaborative discourse.

Acknowledgments

Thanks to David DeGrazia, Tom Beauchamp, and Patrick Birkel for very helpful comments.

Notes

1. John Rawls, *A Theory of Justice* (Cambridge, MA: Harvard University Press, 1971), 12, 136–42.
2. Derek Parfit, *Reasons and Persons* (Oxford: Oxford University Press, 1984).
3. Julian Savulescu, “Bioethics: Why Philosophy Is Essential for Progress,” *Journal of Medical Ethics* 41 (2015): 28–33.
4. Julian Savulescu, Iain Chalmers, and Jennifer Blunt, “Are Research Ethics Committees Behaving Unethically? Some Suggestions for Improving Performance and Accountability,” *BMJ* 313 (1996): 1390–93; Julian Savulescu and Merle Spriggs, “The Hexamethonium Asthma Study and the Death of a Normal Volunteer in Research,” *Journal of Medical Ethics* 28 (2002): 3–4; Julian Savulescu, “Harm, Ethics Committees and the Gene Therapy Death,” *Journal of Medical Ethics* 27 (2001): 148–50.
5. Julian Savulescu, “Safety of Participants of Non-Therapeutic Research Must Be Ensured,” *BMJ* 316 (1998): 891–92; Julian Savulescu and Tony Hope, “Ethics of Research,” in J. Skorupski (ed.), *The Routledge Companion to Ethics* (Abingdon: Routledge, 2010), 781–95.
6. Savulescu and Hope, “Ethics of Research.”
7. Savulescu, “Bioethics: Why Philosophy Is Essential for Progress.”
8. Rawls, *A Theory of Justice*.
9. Peter Singer, “Speciesism and Moral Status,” *Metaphilosophy* 40 (2009): 567–81.
10. Shelly Kagan, *How to Count Animals, More or Less*, Uehiro Series in Practical Ethics (Oxford: Oxford University Press, 2019).
11. Brian Tomasik, “How Many Wild Animals Are There?” *Essays on Reducing Suffering* (2009, as edited 2018), <http://reducing-suffering.org/how-many-wild-animals-are-there/>, retrieved 5 October 2018.
12. Derek Parfit, *On What Matters* (Oxford: Oxford University Press, 2011), vol. 1.
13. John Leslie Mackie, “Rights, Utility and Universalization,” in R. G. Frey (ed.), *Utility and Rights* (Minneapolis: University of Minnesota Press,

- 1984), 86–105; Julian Savulescu, “How Do We Choose Which Life to Save? Equality of Access or a Fair Go?” *Current Paediatrics* 12 (2002): 487–92.
14. Patrick Birkel, personal communication.
 15. Peter Singer, “Life’s Uncertain Voyage,” in Philip Pettit, Richard Sylvan, and Jean Norman (eds.), *Metaphysics and Morality: Essays in Honour of J. J. C. Smart* (Oxford: Blackwell, 1987).
 16. Michael Tooley, “The Moral Status of the Cloning of Humans,” in J. M. Humber and R. F. Almeder (eds.), *Human Cloning: Biomedical Ethics Reviews* (Totowa, NJ: Humana Press, 1998).
 17. Marcus Schultz-Bergin, “The Dignity of Diminished Animals: Species Norms and Engineering to Improve Welfare,” *Ethical Theory and Moral Practice* 20 (2017): 843–56.
 18. Frederick B. Hutt, *Genetics of the Fowl* (New York: McGraw-Hill, 1949), as cited in M. N. Romanov, “Genetics of Broodiness in Poultry: A Review,” *Asian-Australasian Journal of Animal Science* 14 (2001): 1647–54.
 19. Julian Savulescu, “The Nature of the Moral Obligation to Select the Best Children,” in Akira Akabayashi (ed.), *Future of Bioethics: International Dialogues* (Oxford: Oxford University Press, 2014), 170–82.
 20. J. L. Coleman and C. W. Morris, eds., *Rational Commitment and Social Justice: Essays for Gregory Kavka* (Cambridge: Cambridge University Press, 1998).
 21. Owen Schaefer and Julian Savulescu, “The Ethics of Producing in Vitro Meat,” *Journal of Applied Philosophy* 31 (2014): 188–202.
 22. Julian Savulescu, “The Structure of Ethics Review: Expert Ethics Committees and the Challenge of Voluntary Research Euthanasia,” *Journal of Medical Ethics* 44 (2018): 491–93.
 23. James Yeates and Julian Savulescu, “Companion Animal Ethics: A Special Area of Moral Theory and Practice?” *Ethical Theory and Moral Practice* 20 (2017): 357–59.
 24. Peter Stubley, “Teacher Who Fed Live Puppy to Turtle in Front of Pupils Charged with Animal Cruelty,” *Independent*, <https://www.independent.co.uk/news/world/americas/puppy-fed-snapping-turtle-school-teacher-robert-crosland-preston-junior-high-idaho-a8381146.html>, retrieved 5 October 2018.
 25. Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 8th ed. (New York: Oxford University Press, 2019); 1st ed. published 1979.

Biographical Information on the Authors and Commentators

About the Authors

Tom L. Beauchamp

Tom Beauchamp is Professor Emeritus of Philosophy in the Philosophy Department and the Kennedy Institute of Ethics, Georgetown University, where he was appointed in 1970. In 1975, he joined the staff of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, where he drafted the bulk of this commission's *Belmont Report* (first published 1978). He served a term as a member of the Council of the Institute of Laboratory Animal Research (ILAR), a part of the National Academy of Sciences in the United States, where he helped to revise the *Guide for the Care and Use of Laboratory Animals* (in an edition prior to the current edition).

He is one of five authors of *The Human Use of Animals: Case Studies in Ethical Choice* (2nd ed. 2008), a body of original case studies combined with ethical analysis. He is coeditor (with R. G. Frey) of the *Oxford Handbook of Animal Ethics* (2011). He is also coauthor (with his longtime collaborator James F. Childress) of *Principles of Biomedical Ethics* and coauthor (with bioethics scholar Ruth R. Faden) of *A History and Theory of Informed Consent*. His major published articles on the place of principles in biomedical ethics were collected and republished in 2010 by Oxford University Press under the title *Standing on Principles: Collected Works*.

In 2011, Dr. Beauchamp received the Lifetime Achievement Award for Excellence in Research Ethics by Public Responsibility in Medicine and Research (PRIM&R), the primary U.S. association for teaching and research in both animal and human research ethics. In 2010, he was presented the Henry Beecher Award of the Hastings Center, New York, for a lifetime of contributions to research ethics and other areas of bioethics. In 2004, he received the Lifetime Achievement Award of the American Society of Bioethics and Humanities (ASBH) in recognition of outstanding contributions and significant publications in bioethics and the humanities.

David DeGrazia

David DeGrazia holds degrees in philosophy from the University of Chicago (B.A.), Oxford University (M.St.), and Georgetown University (Ph.D.). He is Elton Professor of Philosophy at George Washington University, where he has taught since 1989, and Senior Research Fellow in the National Institutes of Health Department of Bioethics, which he joined on a part-time basis in 2013. In 1996, he helped draft the NASA Principles for the Care and Use of Animals. In 2012, he served as Senior Adviser to the staff of the U.S. Presidential Commission for the Study of Bioethical Issues in its development of a report, *Safeguarding Children: Pediatric Medical Countermeasure Research* (published in 2013). In 2018, he received George Washington University's Office for the Vice President of Research Distinguished Scholar Award.

Dr. DeGrazia's research has been supported by major grants from the American Council of Learned Societies, the National Endowment for the Humanities (twice), and the National Institutes of Health (prior to his employment at NIH). His scholarly work on animals addresses their moral status, their consciousness and cognitive capacities, and the ethics of using animals in research and for food. His animal-focused publications include *Taking Animals*

Seriously: Mental Life and Moral Status (New York: Cambridge University Press, 1996); *Animal Rights: A Very Short Introduction* (Oxford: Oxford University Press, 2002), which has been republished in eight foreign languages; and more than two dozen solo-authored journal articles and chapters in anthologies. His other books include *Human Identity and Bioethics* (New York: Cambridge University Press, 2005), *Creation Ethics: Reproduction, Genetics, and Quality of Life* (New York: Oxford University Press, 2012), and, with Lester Hunt, *Debating Gun Control* (New York: Oxford University Press, 2016). DeGrazia's articles have appeared in such journals as *Philosophy & Public Affairs*, *Ethics*, *Hastings Center Report*, *Public Affairs Quarterly*, and *Pain*. His article "The Ethics of Animal Research: What Are the Prospects for Agreement?" has been reprinted in several anthologies.

About the Commentators

Larry Carbone

Larry Carbone is Director of Animal Care and Use in the program office at the University of California, San Francisco. He has worked as a veterinarian with laboratory animals for more than thirty years. Dr. Carbone holds both a D.V.M. and a Ph.D. in History and Philosophy of Science and Technology from Cornell University, as well as specialty board certifications in the American College of Laboratory Animal Medicine (ACLAM) and the American College of Animal Welfare. He has worked extensively on the responsibilities of institutional animal care and use committees (IACUCs) and on improving animal welfare in laboratories.

Dr. Carbone's book, *What Animals Want: Expertise and Advocacy in Laboratory Animal Welfare Policy*, was published in 2004 by Oxford University Press. An example of his influential practical work on pain management is "Pain Management

Standards in the Eighth Edition of the *Guide for the Care and Use of Laboratory Animals*,” *Journal of the American Association of Laboratory Animal Science* 51, no. 3 (2012): 322–28. He has lectured regularly on how to improve IACUC meetings, pain management, the advantages of strong writing for animal welfare and science, and the possibility of achieving consensus on controversial animal studies.

Frans B. M. de Waal

Frans de Waal is a Dutch American biologist and primatologist whose research concentrates on primate behavior and social intelligence and on animal conflict resolution. He is C. H. Candler Professor in the Psychology Department of Emory University and Director of the Living Links Center at the Yerkes National Primate Research Center in Atlanta. He has been elected to the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the Royal Dutch Academy of Sciences. In 2007, he was selected by *Time* magazine as one of the World’s 100 Most Influential People Today.

Dr. De Waal has drawn many parallels between nonhuman primate and human behavior in relation to peacemaking, morality, and the emotional effects of trauma. The titles of two of his edited volumes articulate two of his main interests: *The Primate Mind* (2012) and *Evolved Morality* (2014). The topics of his research include empathy and cooperation, inequity aversion, and social cognition in chimpanzees, bonobos, macaques, elephants, and other species. His *Peacemaking among Primates* (1989) received the Los Angeles Times Book Award; and, with the wildlife photographer Frans Lanting, he produced the first overview of bonobo behavior in *Bonobo: The Forgotten Ape* (1997). Throughout his career he has worked at zoos and primate centers, conducting noninvasive studies of the social lives of primates.

Rebecca Susan Dresser

Rebecca Dresser is Daniel Noyes Kirby Professor of Law Emerita at the Washington University School of Law (St. Louis), where she has regularly taught a seminar titled Biomedical Research Law and Policy. She earned a J.D. at Harvard University in 1979. Between law school and her arrival at Washington University in 1998, Professor Dresser completed a postdoctoral fellowship at the National Institutes of Mental Health, clerked for U.S. District Court Judge James E. Doyle, and taught at the University of Chicago Law School, Baylor College of Medicine, and Case Western Reserve Law School. She also completed a fellowship in the Program for Ethics and the Professions at Harvard University. Professor Dresser served on both the President's Council on Bioethics and the National Institutes of Health Recombinant DNA Advisory Board, two distinguished national bodies on research ethics and public policy in the United States.

Professor Dresser's extensive writing profile includes coauthorship of a casebook on bioethics and law and of a book on the ethical treatment of animals. She has devoted much of her career to topics in human and animal research ethics. She is the sole author of *Silent Partners: Human Subjects and Research Ethics* (Oxford University Press, 2016) and *When Science Offers Salvation: Patient Advocacy and Research Ethics* (Oxford University Press, 2001).

Joseph P. Garner

Joseph Garner is Associate Professor of Comparative Medicine and, by courtesy, of Psychiatry and Behavioral Sciences at the Stanford University Medical Center. He received his D.Phil. from the Department of Zoology at the University of Oxford in 1999, did postdoctoral research in animal behavior and well-being at the University of California–Davis, served on the faculty in the

Department of Animal Sciences at Purdue University, and joined the Department of Comparative Medicine at Stanford in 2011.

Dr. Garner's research interests include the development of refined methods in behavioral research; abnormal behaviors in animals; mouse well-being and enrichment; and the scientific impact of well-being problems in laboratory animals. One goal of his work is to understand why most drug and other results of animal studies fail to translate into human outcomes and how changes in animal research can help resolve this problem. His laboratory work in developmental neuroethology addresses issues in human and animal well-being. In addition, he is interested in developing methods and underlying psychobiological principles to predict and prevent abnormal behavior in animals and mental disorders in humans. His current work includes experimental design, reproducibility, and translatability; aggression and other welfare issues in laboratory mice; designing automated environments to improve data quality and welfare; and interdisciplinary collaborative work in human health.

Brian Hare

Brian Hare is Associate Professor of Evolutionary Biology at Duke University; a member of the Center for Cognitive Neuroscience, Duke Institute for Brain Sciences; and founder of the Duke Canine Cognition Center. He received his Ph.D. from Harvard University and founded the Hominoid Psychology Research Group at the Max Planck Institute for Evolutionary Anthropology (Leipzig, Germany) before arriving at Duke. Much of his research involves comparisons of human behavior with nonhuman primate and canine behavior.

Dr. Hare's research involving animal subjects includes extensive work outside of laboratories. He studied the cognition of great apes in several African sanctuaries, including chimpanzees

at Tchimpounga and Ngamba Island and bonobos at Lola ya Bonobo. He has researched lemur cognition at the eighty-acre Duke Lemur Center. And he cofounded Dognition, a unique research program in which dog owners play a variety of games with their dogs, at home, to test their cognitive skills. With Vanessa Woods, Dr. Hare coauthored *The Genius of Dogs*. With Shinya Yamamoto, he coedited another book, *Bonobo: Unique in Mind, Brain, and Behavior*. In 2004, he received the Sofja Kovalevskaja Award, Germany's most prestigious award for young scientists. In 2007, *Smithsonian* magazine named him one of the top American scientists under the age of thirty-six.

Margaret S. Landi

Margaret Landi has served as Chair of the Institute for Laboratory Animal Research (ILAR) Council of the U.S. National Academy of Sciences and is currently Chief of Animal Welfare, Ethics, and Strategy for GlaxoSmithKline Pharmaceutical Co. Her role as Chief Veterinarian for GSK is to provide leadership and set policies for animal usage. Her responsibilities include ensuring that the quality of work with animals is independent of study venue in order to promote consistency in practices across animal care and use programs at GSK sites around the world. She has recently published and lectured on the application of global principles for laboratory animals in an international arena featuring differing laws, cultures, regulations, and policies.

Dr. Landi is a Diplomate in the American College of Laboratory Animal Medicine (ACLAM) and Past President of the organization. She has served on review committees of the National Institutes of Health (NIH), has led special site visit teams for NIH committees, and was an ad hoc member of the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC). She has a V.M.D. from the University of Pennsylvania, a masters in

Comparative Medicine from Penn State University, and a masters in Bioethics from the University of Pennsylvania.

Julian Savulescu

Julian Savulescu holds doctoral-level degrees in both medicine and philosophy. He is Uehiro Chair in Practical Ethics and Director of the Oxford Uehiro Centre for Practical Ethics at the University of Oxford, is Co-Director of the Wellcome Centre for Ethics and Humanities, and was Editor of the *Journal of Medical Ethics*, 2001–2004 and 2011–18. He is also Visiting Professorial Fellow in Biomedical Ethics, Murdoch Children's Research Institute, Australia, and Distinguished Visiting Professor in Law at the University of Melbourne. He is coauthor of *Medical Ethics and Law, Unfit for the Future*, and *Ethics, Conflict and Medical Treatment for Children*.

Professor Savulescu's interests in neuroscience, genetics, enhancement, and stem-cell research pertain to research with both human and animal subjects. He has published on the ethics of genetically modified animals, including the creation of hybrids and chimeras; the experimental use of animals such as pigs for purposes of growing human organs; the moral status of animals enhanced with higher-level cognitive capacities; and the ethical review and regulation of research involving genetically modified animals.

Index

- absolute principles and rules, 56
- activists, 87
- aggression
 - allegedly present in laboratory primates, 105, 111n13
 - human, 105
 - in laboratory mice, 152
- alternatives (alternative methods)
 - to chimpanzee research, 102
 - ethically obtainable results, using alternative methods, 7
 - nonanimal methods and resources as, 13
 - simple and readily available, 93
 - Three Rs connection to the idea of, 22, 40n28, 40n29
 - See also* the Three Rs approach
- analgesia, 16, 57, 83, 91, 93
- anesthesia, 16, 31n13, 56, 57, 83, 93
- animal care and use committees (ACCs and IACUCs). *See* committees for ethics review (ACCs, IACUCs)
- animal minds: mental state
 - attributions by humans, 105
- animal models in research, 2, 8, 53–54, 64, 74, 80, 90, 97n22
- animal-protection community. *See* two communities: animal research and animal protection
- animal-research community. *See* two communities: animal research and animal protection
- animal rights groups, 71
- animals' responses to stressors. *See* stress
- animal welfare. *See* welfare interests
- anxiety, 16, 82, 86. *See also* fear
- apes, 62–64, 66–67, 153. *See also* bonobos; chimpanzees; gibbons; gorillas; orangutans
- arthropods, 62
- automatons, animals conceived as, 62
- autonomy, principle of respect for, 119, 144
- basic needs
 - AALAS statement on requirements to meet, 33n17
 - their centrality to animal welfare ethics, 32, 129
 - differing among species, 118
 - examinations of by research review committees, 101, 118
 - failures to meet, 12, 18, 20, 22, 92, 118, 124n21, 142
 - principle of, 3, 11–12, 14–16, 18, 92, 128, 136–138, 142–143
 - See also* committees for ethics review (ACCs, IACUCs)
- basic research, 8, 59n4, 119
- behavioral research, 1, 27n5, 76n2
- Belmont Report*, 1, 69, 130
- beneficence, 119, 128, 140, 142–143, 144
- benefit-risk assessments and comparisons
 - in basic research, 8

- benefit-risk assessments and
 - comparisons (*cont.*)
 - benefits, costs, and risks of animal research, vii, 8, 62
 - expected net benefit, 7, 8, 70, 103
 - and meeting cost-benefit requirements, 86
 - no common currency for
 - comparing risks and benefits, 49–50
 - pain-to-gain balancing in, 62
- Bentham, Jeremy, 122n9
- biases that influence perception, 86, 104–105
- biology, 2, 48, 52–53
- birds, 15, 28n7
- bonobos, 107, 109n5
- boredom, 16
- breeds and breeding, 80–81, 104–105, 139–140
- Burch, Rex L. See *Principles of Humane Experimental Technique*
- cages for confinement, 16, 52, 65–66, 93, 96n15, 123n14
- cancer research and protocols, 50, 53–54, 59n4, 59n8, 60n10, 89–90
- captivity, 5, 103, 106, 115
- Carbone, Larry, 149–150
- caretakers' obligations, 14
- cats, 58n3, 144
- cell cultures, 7
- cephalopods, 15, 28n7
- chimpanzees
 - legal status of, 63
 - in research, 63–64, 100, 102, 103–104, 108, 109n5
 - social relations among, 66–67
- cognition
 - cognitive abilities of animals, 61–62
 - continuity in, across humans and other species, 62
 - creating impairment in, 150
 - in dogs, 106–107
 - in mice, 93
 - theory of mind and, 62
- committees for ethics review (ACCs, IACUCs)
 - analysis of the social benefit of studies by, 55, 84
 - changes needed in practices of, 73–75
 - conflicts of interest in, 19
 - consensus in committee evaluations, 2
 - cultural norms in, 83–84
 - data analysis plans and, 87–88
 - duties of members of, 19, 83
 - their focus primarily on animal welfare, 38n26, 51–52, 84
 - their function of assessing scientific merit and standards, 75, 84
 - increasing the diversity of membership on, 75
 - justifications required to be provided by, 6
 - lack of comprehension of pain in, 106
 - limitations of the work in, 50–52, 72–75, 101, 113–114
 - national standards recommended for, 57
 - need to proactively question procedures in, 81–84, 91–94, 114
 - as overseeing more than pain and distress, 57, 84–85, 94n3
 - as part of an essential oversight system, 70–71
 - regulatory structures and, 79, 85
 - responsibility to ensure best practices are followed, 86–87, 90

- setting limits on the number of animals used, 76
 - ways to improve work in, 38–39, 46, 51–55, 85–88, 93–94
- common ground for examining animal research ethics, 2, 94, 119
- companion animals in research, 102.
 - See also* cats; dogs
- compassion for animals, crucial importance of, 99–100, 105, 108–109
- computer models, as alternatives to animal testing, 7, 131. *See also* alternatives; animal models
- confinement, 16, 52, 66. *See also* cages for confinement; deprivation; freedom
- conflicts of interest, 19
- consciousness, 46, 47, 140–142.
 - See also* self-consciousness; sentience
- consent to research, 5, 51, 107, 136.
 - See also* voluntary participation in experiments
- coping strategies and capacities, 89
- core values of animal research ethics, vii, 1, 3–4, 101, 115, 127
- costs
 - expected costs, risks, and benefits, 6–9, 18, 47, 142
 - failures in anticipating benefits and costs, 104
 - financial costs and opportunity costs, 7, 103, 108
 - to humans, of animal research, 22
 - imposed by regulatory systems, 71, 109n5
 - meaning of the term, 7
 - of pain management regimens, 52
 - quantitative scores of, by ethics review committees, 51
 - and study design, 86
 - and the Three Rs framework, vii, 4
- crustaceans, 29n7
- Darwin, Charles, 99, 101
- de Waal, Frans B. M., 150
- dependence of animal subjects, 5, 14
- deprivation
 - of basic needs, 22, 92–93
 - sleep, 16
 - sustained and inescapable forms of, 36n23
 - of water, 92–93, 94, 118, 126
- discomfort, 13, 16, 36n23. *See also* distress; pain; suffering
- diseases
 - causing, in laboratory animals, 53, 59n8, 139
 - cure or treatment of, in humans, 48–50, 59n4, 90–91
 - freedom from, in animal subjects, 13–15, 129
 - vaccination for, 114
- disgust toward laboratory animals, 108
- distress
 - degrees of, when animals are harmed, 49
 - ethical thinking as informing best practices for control of, 84
 - freedom from, 15–16, 129
 - institutional guidelines for controlling, 19, 21–22, 51
 - Three Rs framework on, 2, 21–22, 47
 - upper limits to levels of, 17, 47
 - when it amounts to unnecessary harm, 12–13, 52–56, 84
 - See also* discomfort; pain; stress; suffering; upper limits of permissible harm in research
- dogs, 58n3, 79, 99–100, 102, 104, 106–107, 144

- dolphins, 63
- Dresser, Rebecca, 151
- drugs, in research, 55–57. *See also*
medicines, in research
- ecology of animal well-being, 67,
105–106
- economic considerations. *See*
financial problems in animal
research and review
- elephants, 62, 150
- emotions
 - of disgust, 108
 - capacities for, in animals, 16, 61
 - reunion of, 67
 - study of animal, 61
 - See also* fear; suffering
- empathy, 61
- endangered populations, 107
- environmental enrichment for
animals, 34n17, 88–91,
96n20, 121n8
- errors in animal testing regarding
toxicity and efficacy
 - false efficacy negatives, 8, 117
 - false efficacy positives, 8
 - false toxicity negatives, 8
 - false toxicity positives, 8
- ethologically appropriate
environments, 34n17
- E.U. Directive 2010, 29n7,
36nn23–24, 56
- euthanasia, 15–16, 35n20, 54, 59n3
- evolutionary connections between
humans and nonhumans, 61
- exercise for animals involved in
research, 15, 129
- exhaustion in animals, 16
- experimentation
 - enforcing standards in
experimental design, 85–89,
95n7, 114
 - evaluation of, 49–53, 55
 - experimental procedures,
16–17, 80–83
 - experimental techniques, humane,
21–22, 31n13, 36n23, 37n25,
40n28, 80, 127
 - voluntary participation in,
66, 107
 - See also* research
- extinction, 100, 108
- factory farming, 143
- fear, 13, 16, 61, 82. *See also* anxiety
- financial problems in animal
research and review
 - financial costs and opportunity
costs, 7, 103, 108
 - limits to funding, 50, 76
- fish, 28n7, 58n3, 62, 90, 144
- food, 13, 15, 52, 93, 101, 107, 118,
137–138
- frameworks of moral principles
 - in the *Belmont Report*, 1
 - comprised of nonabsolute
principles, 83
 - core values underlying justified, 3
 - function of, 83
 - in the Three Rs conception, vii, 2,
21–23, 113
 - See also* principles, as a framework
for animal research ethics
- freedom
 - from controls, welfare
importance for animals
of, 88–89
 - from harms, 15, 34n19, 129, 136
 - of movement, 15, 129
- frustration in animals, 16, 93
- Garner, Joseph P., 151–152
- gibbons, 109n5
- global concern with animal
welfare, 11
- gorillas, 109n5

government regulations. *See*
regulations (government)

Hare, Brian, 152–153

harm

degree(s) of, 47, 49, 115, 122n10
freedom from, 15, 34n19, 129, 136
justification for, in research, 2,

5–6, 47, 101–102, 114

measuring severity of, 16–17

minimal, as research policy, 13–

14, 17–18, 22, 23n1, 47, 54–55,
84–85, 102

principle of no unnecessary harm,
3, 12–13, 16, 18, 52–56, 84, 92,
118, 128

principle of sufficient value to

justify harm, 3, 7, 9–10, 48, 52,
55, 62, 116, 128

psychological, 16

scales of low to high pain caused
to animals, 49, 53

scientific necessity as a

justification for causing, 20–21

upper limits of permissible, 3, 12,
16–18, 53, 56–57, 102–103,
128, 138

See also discomfort; distress;
pain; stress; suffering

housing for animals in research

conditions of, 10, 13, 16–17, 33n17

often overlooked as a problem, 80

social housing, 65–67, 73, 89

species-specific, 118

husbandry, 80

impartiality in judgments, 19, 132

inspection of facilities,

requirements of, 19

institutional animal care and use

committees. *See* committees

for ethics review (ACCs,

IACUCs)

interests of animals. *See* welfare
interests

justification, moral

of animal research, as seen in two
communities, 2

essential place of, in animal
research ethics, 5–6

in ethics review committees, 5

for harming animals in
research, 114

necessary conditions of justified
animal research, 6–9, 23,
101–102

scientific necessity as a
justification for the use of
animals, 20–21

six principles stating necessary
conditions of justified
research, 6

Landi, Margaret S., 153–154

legislation, 31n13, 79, 104

machines, animals interpreted
as, 62

mammals, 15, 28n7

maternal separation, 16

measuring

bias that influences data in, 86

cortical activity and pain, 107

and perception of pain and

suffering, 105–106

severity of harm, 16–17

welfare, 107

medicine, including veterinary

medicine (the professions of)

animal models in, 90

codes of ethics for, vii

public policy and, 27n5, 63

medicines, in research, 8, 55. *See also*

drugs, in research

mice, 53, 58n3, 79, 86, 89–93

- minimal harm as a research policy,
13–14, 17–18, 22, 23n1, 47,
54–55, 84–85, 102. *See also* the
Three Rs approach
- monkeys, 46, 58n3, 63, 65–66,
101, 132
- moral blindness, 105
- moral status
accounts of rarely grounded in a
comprehensive theory, 62–63
arguments supporting animals', 10
challenges to traditional thinking
about, 1
human status viewed as higher, 2
large brains as a basis of, 62–63
levels of, 9, 10
no single dimension of, 100
sentience as a basis of, 2, 9, 63
as setting limits to the use of
animals, 2
similarity to humans as a basis of,
63, 114
- motives in animal research
of animal welfare scientists, 82
in cognition experiments, 92–93
conflict of, in both helping and
using animals, 100
- necessary conditions of justified
animal research, 6–9, 23,
101–102
- neglect of obligations and
negligence, 13–14
- obligations
based on moral principles, 2, 6–7,
11–12, 84, 105
of caretakers of animals, 14
of ethics committees, 11, 131
and the moral status of animals,
30n10, 117
welfare interests as
determining, 2, 11
- See also* committees for ethics
review (ACCs, IACUCs);
committees for ethics review;
neglect of obligations and
negligence
- orangutans, 109n5
- pain
animals' similarity to humans in
experiencing, 12–13
capacity to experience, 62
creating animals that do not feel
pain, 139–141
decreasing the amount of, 21–22
exceptions to rules against
causing, 13, 56
freedom from, as a basic
need, 15–16
full veterinary treatment of, when
inflicting, 55
and helplessly paralyzed
animals, 56
management of, 51–52, 55
mitigated and unmitigated, 49
need for expert knowledge of, 46
painkillers and their effects, 52
perception by humans of pain in
animals, 104–105
and scales of low to high harm to
animals, 49, 53
untreated and undertreated, 52, 55
upper limits of permissible, 3, 12,
17–18, 45, 53, 56–57, 102–103,
118, 138
without postsurgical analgesia, 57
- primates
in laboratories, perceived as
aggressive, 105, 110n13
psychological well-being of, 16,
31n13, 35n22, 122n13
social housing for, 65–67
social and mental lives of, 61
water deprivation of, 118

- See also* apes; monkeys; rhesus macaques in laboratories
 principles, as a framework for animal research ethics
 challenges for the implementation of, 70
 principle of basic needs, 3, 11–12, 14–18, 20, 22, 70, 92, 101, 106, 118, 128
 principle of expected net benefit, 3, 7–10, 70, 102, 116–117
 principle of no alternative method, 3, 6, 7, 9, 13, 116, 128
 principle of no unnecessary harm, 3, 12–13, 16, 18, 52–54, 92, 118, 128
 principle of sufficient value to justify harm, 3, 7, 9–10, 48, 52, 55, 62, 116, 128
 principle of upper limits to harm, 3, 12, 16–18, 20, 53, 56–57, 102–103, 128, 138
 principles of animal welfare, 3, 9, 11–18, 23, 81–82, 90–91, 115, 143
 principles of social benefit, 3, 6–10, 12–14, 22–23, 54, 81–82, 84, 89–91, 117, 128
Principles of Humane Experimental Technique
 interpreted as a body of regulatory principles, 81
 limitations of the account of principles in, vii, 22–23, 47, 54, 80–81, 127
 Russell and Burch, the authors of, vii, 21–22, 47, 54, 69, 72, 80–81, 127
 the source of the Three Rs approach, 21–22
 as a system of alternatives to conventional research programs, 21–22, 40n28, 40n29
 three principles in, 21–22, 47, 54
 See also the Three Rs approach
 protocols, ethical evaluation of, 2, 5–7, 18–19, 24n2, 38n26, 84, 87, 114, 124n21, 130. *See also* committees for ethics review (ACCs, IACUCs)
 psychological harm, 16. *See also* distress; harm; pain; suffering
 public concerns about animal welfare, 1, 108
 randomization and experimental design, 85–87
 rats, 63–64, 79, 89
 reason, faculty of. *See* cognition
 reduction of number of animals used. *See* the Three Rs approach
 refinement, principle of. *See* the Three Rs approach
 regulations (government)
 assumptions made in, 47, 115
 distinguished from ethics, 79–81, 84
 globally in place for animal research, vii, 3
 history of, in several countries, 31n13, 71
 as prohibiting unnecessary harm, 54
 as protecting the interests of animals, 10
 on the psychological well-being of primates, 35n22
 species affected by, 16
 specification of, by ethics committees, 19, 84, 94
 See also committees for ethics review (ACCs, IACUCs)
 replacement, principle of. *See* the Three Rs approach

- reproducibility problems in
 research, 85, 87, 121n7. *See also* translatability of research,
 nonhuman to human
- research. *See* alternatives; basic
 research; behavioral research;
 cancer research and protocols;
 chimpanzees in research;
 companion animals in research;
 consent to research; core
 values of animal research
 ethics; drugs, in research;
 experimentation; financial
 problems in animal research
 and review; housing for
 animals in research; minimal
 harm as a research policy;
 necessary conditions of justified
 animal research; principles,
 as a framework for animal
 research ethics; reproducibility
 problems in research;
 the Three Rs approach;
 two communities: animal
 research and animal protection
- review and oversight of experimental
 procedures. *See* committees
 for ethics review (ACCs,
 IACUCs)
- rhesus macaques in laboratories,
 64, 101
- rights, 31n13, 63, 71
- risk(s). *See* benefit-risk assessment;
 costs; harm
- rodents. *See* mice; rats
- rules. *See* principles, as a framework
 for animal research ethics;
*Principles of Humane
 Experimental Technique*; the
 Three Rs approach
- Russell, William M. S. *See* *Principles
 of Humane Experimental
 Technique*
- safety, 121n5
- sanctuaries, 58n3, 64, 107
- Savalescu, Julian, 154
- scholarship in animal ethics, 1
- scientific necessity as a justification
 for causing harm, 20–21
- scientific study of animals, 1, 23
- self-consciousness, 46, 137–138,
 141–142
- sentience
 animals' similarity to humans
 in, 13, 15
 meaning and scope of the
 term, 28n7
 and moral status, 2–3, 9, 11, 47,
 62–63, 120n3
 and subjective quality of life, 11,
 16, 28n7
- speciesism, 47
- statistics
 lack of understanding of in some
 research, 85–86
 minimum requirements of
 statistical analysis, 83–84
 statistically significant data, 48
- stress, 5, 13, 16, 82, 86, 88–90, 92,
 107. *See also* distress
- suffering
 animals' similarity to humans in,
 13, 133
 Darwin on human feelings about
 animals', 99
 freedom from, as a basic need,
 15–16, 129
 goal of minimizing, 13–14, 17–18,
 22, 47, 54–55, 84–85, 102
 hidden forms of, 16, 106
 how to reduce, 108, 139
 invalidation of scientific data
 caused by, 34, 53
 justification of causing,
 proportionate to degree of
 harm, 47

- as justified by social and scientific purposes, 70
- and moral status, 10
- objective measures of, 107
- severe forms of, 12, 16–18, 33n16, 56, 70
- and speciesism in standards and regulations, 47, 49
- and states of well-being, 11
- study of, 82
- and the Three Rs approach, 2
- unavoidable causation of, 13, 101
- upper limits to, 12, 16–18, 45, 56
- See also* distress; pain; the Three Rs approach
- the Three Rs approach
 - animal-research and animal-protection views of, 2–4, 113–114, 116, 119
 - connection to the idea of alternatives in, 7, 22, 40nn28–29, 102
 - framework of principles in, vii, 2, 21–22, 47, 54, 113
 - insufficiently responsive to issues of moral status, 221–222, 47
 - interpreted as a body of regulatory principles, 81
 - limitations of, vii, 22–23, 47, 54, 80–81, 127
 - received as a canonical moral statement, vii
 - and reduction of harm to animals, 2, 21–22, 47
 - Russell and Burch, as the authors of, 21
 - on suffering and its reduction, 2
 - thresholds of pain and suffering. *See* upper limits of permissible harm in research
 - translatability of research, nonhuman to human, 74, 85, 87, 90–91, 95n7, 114, 121nn6–8. *See also* reproducibility
 - problems in research
 - transportation of animals, moral problems in, 5, 11, 13, 16–17
 - trauma, 150
 - two communities: animal-research and animal-protection
 - common ground between, vii, 2–3, 113–114, 116, 119
 - differing views on the Three Rs approach, 2, 4
 - perceived as irreconcilable, 1–2
 - possible consensus of values between, vii, 4, 69
 - upper limits of permissible harm in research, 3, 12, 16–18, 53, 56–57, 102–103, 128, 138
 - utilitarian moral theory, 30n12
 - vaccines and vaccine trials, 108, 114
 - values, basic or core, vii, 1, 3–4, 69, 101, 127
 - vertebrate animals, 15, 28n7, 62, 133
 - veterinarians
 - appropriate practices of euthanasia for, 35n20
 - involved in research, 45, 47, 50, 52–54
 - perceptions of pain sensitivity in animals among, 104–105
 - reliance on regulatory structures by, 79
 - roles and obligations of, 11, 47, 51–52, 73, 87
 - See also* principles, as a framework for animal research ethics
 - veterinary medicine, vii, 59n4
 - violent behavior in animals (alleged), 111n13
 - vivisection, 99

- voluntary participation in
 - experiments, 66, 107
- vulnerability of animal subjects, 5
- water deprivation procedures in
 - research, 92–93, 94, 118, 126
- welfare interests
 - of animals, 2, 10, 28n7, 32n14
 - as determining professional
 - obligations in research
 - involving animals, 2, 11
 - government regulations as
 - protecting animals', 10
 - human and animal, 9–10
 - meaning of the term
 - “interest,” 32n14
 - and principles of animal welfare,
 - 3, 9, 11–18, 23, 81–82, 90–91, 115, 143
 - See also* committees for ethics
 - review (ACCs, IACUCs); core values; freedom
- zoonotic disease transmission, 108
- zoos, 61, 107