Chapter 26
The Use of Animals in the Study of Human Disease: Key Roles of General Ethical Principles

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Abstract This chapter presents and defends key ethical principles for the use of animals in the scientific study of human disease. The discussion focuses on the roles that general ethical principles, and sets or collections of such principles, play in this research. Because of the importance and wide applicability of general principles in ethical assessment of human health-related animal research, the chapter is able to provide a useful overview of ethical issues raised by this research. The chapter discusses the roles that sets of general principles play in providing ethical guidance to those involved in this research, and in expressing their central obligations and ideals. The chapter identifies the ethical core of human health-related animal research: the basic general ethical principles that govern its use and care of animals.

Keywords Human disease · Animals · Welfare · Ethical principles · Health

Introduction

Aims of the Chapter

This chapter presents and defends key ethical principles for scientific research that employs animals to understand, and ultimately to prevent, alleviate, and cure diseases that afflict humankind. The discussion also identifies a number of ethical and empirical issues that these principles involve or imply and that need further consideration. The chapter aims to provide readers who may not be closely familiar with human health-related animal research, as well as those who are involved in this research, a useful account of the importance of general ethical principles in this crucial part of the battle against human disease.

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Preliminary Definitions and Considerations

In discussing *ethical* issues and principles relating to the use of animals in the study of human disease, the chapter considers issues and principles that pertain to whether animals so employed are treated in ways that accord with human ethical obligations *to these animals*. Some ethical questions raised by the use of animals in health-related research do not pertain directly to whether animals are used or treated properly. Among such issues presented, for example, by the genetic engineering of animals with organs that can be transplanted to humans (xenotransplantation) are whether these organs would create unacceptable risks of infectious disease for transplant recipients, close contacts of recipients, or the general public; and how, if there is a limited supply of such organs, they should be allocated. Issues raised by xenotransplantation that are relevant to the ethics of the use of animals as understood here include whether it is ethically appropriate to use animals to provide organs for humans; whether animals employed in research to understand how to provide these organs are properly treated; and whether animals bred and raised for these organs will be properly treated.

The term "disease" in humans as used in the chapter includes any condition that would be characterized as health-related and can threaten or shorten life, or cause pain, distress, significant discomfort, or disability. Disease as understood here is the central focus of biomedical scientific research generally, which as expressed in the Mission Statement of the US National Institutes of Health (NIH) is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." (NIH, 2017).

As is reflected in the NIH Mission Statement, by the "study" of human disease, the chapter means the pursuit and advancement of knowledge through scientific research that has as its *ultimate* aim the prevention, alleviation, or cure of human disease. It is appropriate and important to characterize the part of the battle against disease conducted by scientists as the *study* of disease. For it is the advancement of *knowledge*, gained by observation or experimentation, that scientists contribute to this endeavor. The chapter does not consider the pursuit and attainment of knowledge for its own sake as a justification for animal research. This justification is accepted by many animal researchers, including many who seek knowledge that will also prevent, alleviate, or cure disease. Moreover, animal research motivated by intellectual curiosity sometimes contributes to advances in battling human disease (Tannenbaum, 2019).

The terms animal "use" and "research" are employed in the chapter interchangeably. The term animal "testing" is often employed as synonymous with "research." This is not in my view helpful, because testing as usually understood involves the use of numbers, often large numbers, of subjects to assess the soundness of a previous hypothesis, or to determine the efficacy or safety of a given substance or

medical procedure or treatment. Much animal research is conducted on relatively few animals and is intended to explore various kinds of hypotheses before anything resembling a "test" can be performed. However, some animal research projects that are properly characterized as tests can be part, and sometimes an important part, of understanding the nature of a disease and how to combat it. Such testing is included in the use of animals or animal research as understood here.

The chapter refers to research described above as "human health-related animal research" or "HHAR." The chapter discusses HHAR conducted in laboratories on animals that are owned or possessed by these facilities for the purpose of research. Such research represents the overwhelming majority of HHAR projects. A relatively small but increasing proportion of health-related animal research is conducted by veterinary clinicians on privately owned animals (usually pet dogs or cats) that is intended to assist these animals or kinds of animals, and is also intended to contribute to understanding the same or similar diseases in humans (Kol et al., 2015; Lairmore & Khanna, 2014).[1] Because of human diseases that originate in or are transmitted to humans by wild animals, an increasing amount of field research is being done on wild animals that aims to understand how such diseases affect humans as well as these animals (Buttke et al., 2015; Kaur et al., 2008). Many of the ethical principles relating to laboratory HHAR apply to HHAR in pets and wildlife (e.g., that any procedure conducted on a research animal should minimize, and wherever possible prevent, experiences of pain or distress). However, these latter kinds of research raise distinctive ethical issues (Baneux et al., 2014; Paul et al., 2015) that cannot be discussed here.

Finally, the chapter includes within the meaning of the term "principles" not only certain very general philosophical or ethical truths, but also practical guidelines and directives that are of immediate use in the design, conduct, and ethical assessment of HHAR. (For a defense of proposed animal research "principles" in a sense that does not include such directives, see Beauchamp & DeGrazia, 2020, pp. 1–41.) Many of the principles examined here require additional principles to clarify their application in the wide range of kinds of experimentation that HHAR encompasses. However, the ethical principles—and more importantly the sets of principles—presented in the chapter are intended to function primarily as practical guides for action.

[1] It is also noteworthy that many vaccines, medicines, and diagnostic and surgical techniques employed by veterinarians to benefit pets and other animals including antibiotics, cancer chemotherapeutic drugs, anti-inflammatory steroids, diagnostic ultrasound, spinal anesthesia, hip replacement surgery, compression plating of complicated fractures, and surgical stapling, were first discovered or developed using animals in research intended to benefit humans (IOM, 1991; Loew, 1988; Quimby, 1998). Continuing contributions to *animal* health provide a derivative and secondary, but by no means unimportant, justification of HHAR.

Importance of Ethical Issues in HHAR

Some might think that ethical issues in HHAR receive a disproportionate amount of attention. It is fair to say that more has been published on ethical issues relating to the use of animals in scientific research than on any other subject in animal ethics. However, far fewer animals are used in HHAR, and in the totality of all animal research, than for other purposes.[2] Moreover, extensive legal regulation and oversight of HHAR in many countries impose significant *ethical* requirements, including minimization of animal pain or distress, meticulous veterinary supervision and care, and enriched environmental conditions (e.g., AniWA, 2008 [Switzerland]; ASPA, 2016 [UK]; AWA, 2015 [US]; AWAR, 2020 [US]; EAA, 2021 [Netherlands]; EU, 2010 [EU]; GAWAR, 2013 [Germany]; NHMRC, 2013 [Australia]; PCAL, 1994 [Israel]; PHS, 2015 [US]; SABA, 2007 [Singapore]; SAWA, 2018 [Sweden]) that are not generally afforded to the vastly larger number of animals used in meat production, for example.

These facts notwithstanding, there are good reasons for those who participate in HHAR and those who benefit from it—which is virtually everyone—to give serious attention to ethical issues in HHAR. Because most HHAR is funded by government (FASEB, 2017), approval by the public that ultimately pays the freight is essential. Yet public support does not appear to be commensurate with the significant health benefits HHAR has produced for so many people.[3] It is therefore important that

[2] Mice and rats represent the vast majority of animals used in HHAR worldwide, at least 90 to 95 and perhaps as much as 99 percent (Carbone, 2004). The US Animal Welfare Act (AWA) covers research on dogs, cats, nonhuman primates, guinea pigs, hamsters, rabbits, and other warm-blooded animals that the US Department of Agriculture (USDA) Secretary may determine (which includes pigs, ferrets, and sheep, for example), but specifically excludes rats, mice, or birds bred for research (AWA, 2015 § 2132(g)). Accordingly, the AWA does not call for the counting of these latter species. Nor does the US statute that covers mice and rats used in NIH or NIH-funded research, the Health Research Extension Act (HREA, 1985). Because the US, the largest user of research animals, does not tally numbers of these species, and the second largest user, the UK, counts the number of research procedures and not animals, it is difficult to estimate with confidence how many animals are used in research generally or in HHAR in these countries or worldwide. Annual estimates for the US range from 25 to over 100 million (Grimm, 2021; Tannenbaum, 2019, pp. 10–11). One study concluded that in 2015, 192.1 million animals were used worldwide for all research purposes (Taylor & Alvarez, 2019). In contrast, the United States Department of Agriculture reports that in 2020 there were slaughtered in US commercial facilities for human consumption 9.346 billion chickens, 227.6 million turkeys (USDA, 2021g), 32.8 million beef cattle, 132.8 million hogs, and 2.23 million sheep and lambs (USDA, 2021e). In 2020 there were also in the US approximately 9.4 million dairy cows (USDA, 2021f) and in April of that year, 392.77 million laying hens (USDA, 2021d).

[3] For example, a 2018 poll of the Swedish public found that 55% supported experiments on animals "for medical purposes," with an additional 24% stating that their support "depends on" (unspecified) circumstances (SRC, 2019, p. 11). A UK poll in the same year found that 65% of the public supported "use of animals in scientific research as long as it is for medical research purposes and there is no alternative." However, support fell from 75% in 2002 (Ipsos MORI, 2018, p. 18). One US poll found that in 2018 47% of the public favored, and 52% opposed, "use of animals in scientific research," (Pew, 2018) A 2021 poll found that in 2021 52% of Americans believed that "medical testing on animals" is "morally acceptable" and 44% that it is "morally wrong." (Gallup, 2021)

animal researchers and those who oversee or regulate their work be able to convince the public that their research is justified. Moreover, although legal regulation of HHAR seeks to ensure minimization of pain and distress and promotion of research animal welfare, virtually all research animals used in laboratories are kept in cages or enclosures and cannot engage in all behaviors typical for their species. Some experience pain or distress. It is surely an ethical truism that any being that can experience pain, distress, or other unpleasant sensations or feelings should not be caused such experiences by those who use them for their own benefit, without an articulatable and sufficient reason. Furthermore, because HHAR is conducted for one of the most admirable and important goals we humans can have—saving human life and preventing and alleviating suffering—anyone associated with HHAR should welcome the task of ensuring that methods employed to attain this highest of goals reflect the highest ethical standards.

Stages of Laboratory HHAR

The central ethical question relating to a laboratory HHAR experiment is whether it is ethically appropriate to conduct the experiment. If an experiment ought not to be done, *whatever* happens to the animals would be unjustifiable. Among questions relevant to the appropriateness of an experiment that can have ethical components are whether what the experiment seeks to learn should be studied by using animals; if so, what species of animals should be used; how many should be used; what kinds of experimental techniques are acceptable; whether animals should be allowed to experience unrelieved pain or distress; and if, when, and how animals should be killed.

These are the kinds of questions that many seem to identify with asking about the appropriateness of an HHAR project. However, there is much more, regarding what happens to animals, to a laboratory experiment than the experiment itself. The typical HHAR project also includes the breeding of animals by a commercial supplier, or in the case of some facilities and species breeding within the facility; transportation of animals to the facility or laboratory; housing of animals when experimental procedures are not being conducted; supervision of animals by veterinary and animal care staff when they are in facility housing; and disposition of animals at the end of the experiment. Ethical issues can arise during any of these stages of a project. Serious consideration of the ethics of an HHAR project, or kind of HHAR, must include attention to all these stages. An ethical failure in one stage could be sufficient to invalidate a project or to require changes. It sometimes may be possible to make a project that is justified even better from an ethical standpoint by making improvements in one or more of the stages other than the experiment itself. The animal research community worldwide pays considerable attention to conditions in which animals are housed and how they are cared for when not under experimentation, because most research animals spend far more time in, and can be affected at least as much by, housing conditions as by what is done in the laboratory.

General Ethical Principles and the Diversity and Complexity of HHAR

This chapter focuses on the articulation and defense of *general* ethical principles for the conduct of HHAR for several reasons.

First, HHAR is an enormously diverse and complex enterprise. There is a wide range of human diseases that animal research has addressed, a wide range of kinds of animals used in this research, and an even wider range of experimental techniques employed in studying these diseases. Some of these diseases and techniques raise distinctive ethical issues regarding their use of animals. And although certain ethical issues relating to HHAR have been and will continue to be raised, new issues continually arise—as animals are used to address new or newly significant diseases, as new research techniques are developed, and as more is learned about how various kinds of experiments affect, and are affected by, the welfare of the animals.

In light of the diversity, complexity, and developing body of ethical issues in HHAR, a relatively brief discussion of these issues must perforce focus on very broad principles that apply to HHAR generally. However, as is demonstrated below, a discussion of such principles is far from a substitute for serious consideration of the ethics of HHAR. Only by identifying broad ethical principles is it possible to organize, and approach in a systematic and useful way, the variety of ethical questions that HHAR can raise. Moreover, for those who are not intimately familiar with HHAR, as well as for those who are, a survey of general ethical principles that govern this research can provide an informative overview of ethical issues in HHAR.

General Principles as Justifications

Another, and related, reason to focus on general ethical principles in HHAR is that, as is the case in all areas of ethics, assessment of particular conduct or kinds of behavior almost always relies on appeal to general principles. For example, after it was learned that paralyzing curariform drugs used to anesthetize human surgical patients did not eliminate their pain but only made it impossible for them to express it, the use of such drugs to restrain research animals during painful procedures was universally condemned and prohibited by law (e.g., AWA, 2015, §2143(a)(3)(C)(iv)); US Principles, 1985, Principle V). Although preventing pain behavior instead of pain is obviously unacceptable, the prohibition of using paralyzing drugs instead of effective anesthesia in HHAR rests on a general ethical principle, which can be called the *pain and distress minimization principle* (and is discussed further below): *When an HHAR project is justified in using animals in any way that has the potential of causing them pain, distress, or other significantly unpleasant sensations or feelings, the project should prevent the occurrence of such sensations or feelings if possible, eliminate them if and when they occur, or minimize them if and when in light of justified experimental aims they must occur.* Moreover, as is discussed below,

this general ethical principle rests for *its* justification on a number of other even more general ethical principles relating to animals in general and research animals in particular. Virtually everything that can be done with animals in HHAR—ranging from when it is appropriate to use animals in the first place and what species to use, to acceptable procedures in experimentation, to proper housing and veterinary care, to what should be done with animals after an experiment is completed—relies for its justification on some, and often more than one, general ethical principle.

General Principles in Sets of Ethical Standards

There are available to investigators a number of *sets* of general ethical principles for HHAR. These collections tend to be brief, consisting typically of no more than a dozen broad principles. They are regarded by many involved in HHAR as useful tools in designing, conducting and assessing the ethical appropriateness of experiments. Having a relatively brief and easily accessible set of principles in one place provides a location as it were in which to find ethical guidance relevant to one's research.

It is the importance of general principles in the justification of practices in HHAR, and the relevance of these principles to wide ranges of typical or recurring practices, that make such sets of principles useful. For example, the pain and distress minimization principle—which appears prominently in some form in all current sets of ethical principles for HHAR—provides justification for more than prohibiting the use of paralyzing drugs. This principle requires various courses of action, depending on the particular facts at hand, whenever *anything* done to or with a research animal in *any* stage of a project can be accomplished by causing no or less pain or distress. The principle requires—among a multitude of things—that animals: are handled by experimenters and research staff as gently as possible; not be physically restrained during an experiment unless necessary and that any restraint is as brief as possible and causes the least amount of pain or distress possible; are given pre- and post-surgical anesthesia or analgesia when consistent with experimental aims; and are killed when necessary for experimental purposes without pain or distress.

Such sets of general ethical principles have been adopted, as official policy, by major professional organizations whose members conduct, or are involved in the care of animals used in, HHAR (e.g., AALAS, 2021; AES, 2020; AHA, 1985; APA, 2012; APS, 2014; ASIH, 2004; ASLAP, 2008; ASP, 2001; CCAC, 1989; FASEB, 2021; ICLAS, 2013; LAVA, 2016; SfN, 2016; SOT, 2008). Investigators need not be a member of a particular group to find its ethical statements applicable to their research. Some of these professional, and other, collections of general principles are intended to apply to animal studies of particular diseases or kinds of diseases (ACS, 2019 [cancer]; AES, 2020 [epilepsy and seizure disorders]; AHA, 1985 [cardiovascular disease]; APA, 2012 [mental illness and behavioral disorders]; SfN, 2016 [neurological disorders]; Tannenbaum, 2017b [epilepsy and seizure disorders]); to

research on general medical conditions that range across diseases (Tannenbaum, 1999 [pain]); to research on certain species (ASIH, 2004 [amphibians and reptiles]; ASP, 2001 [nonhuman primates]); and to investigators (Tannenbaum, 2017a). Some sets of general ethical principles for HHAR or animal research generally have been adopted by government authorities that have the power to compel compliance with these principles by law (e.g., EU, 2010; US Principles, 1985).

General Principles in Statements of Central Obligations and Ideals

The relevance of general ethical principles to wide ranges of practices in HHAR facilitates another very important use of sets or collections of such principles. The sets of ethical principles of the professional organizations cited in the previous section have been adopted in part to serve as expressions of the central ethical obligations and ideals of these groups. These principles assist in educating members about their ethical responsibilities to research animals, and serve as standards that can be used if questions arise about research practices or the behavior of particular members. These sets of principles are also presented as a testament to the seriousness of the commitment of these groups to the ethical conduct of HHAR—and an invitation to the general public and government to expect compliance with these principles. Professional associations spend a great deal of time and effort writing, re-affirming, citing, and when necessary amending, these ethical standards and discuss them regularly at meetings and research seminars. Their role in promoting ethical animal research cannot be overestimated.

An Instructive Example: The US Principles

An instructive example of a set of general principles that is intended to serve as a convenient source of basic ethical standards, and to articulate central ethical obligations and ideals of HHAR, are the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (Principles* or *US Principles).* The *Principles* are set forth in Table 26.1. They are required by law to be applied in all HHAR conducted or funded by the NIH (HREA, 1985; PHS, 2015, para. I) and other US government agencies (e.g., DoD, 2019; NSF, 2019). The *Principles* have been incorporated into the statements of ethical standards of a number of professional organizations (e.g., AALAS, 2012; ASLAP, 2008; SfN, 2016). The *Principles* are the best known, and most often cited, set of ethical principles for HHAR in the US, and perhaps worldwide.

The flexibility and broad applicability of the *Principles* are apparent. The *Principles* are intended to apply to all kinds of animal research, including HHAR, and identify relevance to human health as one of several considerations that can

Table 26.1 U.S. government principles for the utilization and care of vertebrate animals used in testing, research, and training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species.
I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et seq.) and other applicable Federal laws, guidelines, and policies.
II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.
IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.
V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.
VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.
IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group, such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration. (US Principles, 1985)

justify animal experimentation. The *Principles* provide virtually no specific directions. They do not specify, for example, precisely what species or how many animals investigators should employ in various kinds of experiments; when and what sedative, analgesic or anesthetic agents should be used; when and how animals should be killed; what housing conditions are appropriate for the animals in any given project; when and what kinds of veterinary care must be provided to animals in a project; and what kinds of training in the proper use and care of animals must be provided to scientists and staff involved in a project or kind of project. What the general ethical rules in the *Principles* require depends on the particular facts of a project or a kind of HHAR including its aims, methods of research, and species employed.

The *Principles* reflect their intended role of focusing the attention of those who conduct or are directly involved in HHAR on rules that are essential for the ethical conduct of this research. However, significant gaps in the *Principles* detract from their usefulness in addressing a number of important ethical issues. For example, Principles IV through VIII, which constitute the bulk of the document, apply to the *performance* of research projects or to the housing and care of animals in *ongoing* projects and do not relate to how one is to determine whether a given animal experiment, or kind of experiment, is ethically appropriate in the first place. The only principle that addresses this issue directly, Principle II, merely identifies advancing human health (among other aims) as a legitimate goal of animal research and calls upon researchers to give "due consideration" to how a given experiment is relevant to human health. Neither this nor any of the other principles identify factors that should be included in such consideration, or how much weight these factors should be accorded in determining whether an experiment is justified. Although Principles IV through VI identify minimization of animal pain or distress in experiments as obligatory, neither these principles, Principle II or any of the other principles indicate whether and when pain or distress that an experiment might cause could be sufficient to render it ethically unacceptable.

Core General Principles and the Central Ethical Structure of HHAR

Addressing these omissions might well make the *Principles* a more complete and useful set of basic ethical standards or expression of central obligations and ideals of HHAR. Nevertheless, it is important to appreciate that the *Principles*, like the sets of general ethical principles of professional groups referenced above, have limited albeit important roles. These sets of principles can be used as convenient sources of ethical standards, or as statements of central obligations and ideals that can be presented forcefully to researchers and the public, precisely because they are brief. Other than typically beginning, as in the *Principles*, with a statement of the importance of animal research in understanding disease, these sets of principles do not contain even cursory *arguments* for their principles. Nor do they indicate how their various principles follow from or imply other of their principles. Nor do these sets of principles contain supporting commentary that explains why their principles are correct and how they are interrelated. These sets of principles do not do these things because researchers who use them *assume* the correctness of their principles and thus view these principles as reliable *starting points* in designing and conducting experiments or in dealing with colleagues or the public. Those who use these sets of principles also *assume*, and do not look to these principles for a demonstration of, the overall ethical appropriateness of HHAR.

Because of the importance of general principles in the ethical assessment of research practices, and the relevance of some of these principles to wide ranges of typical or recurring practices, it is possible to identify a set of general ethical

principles for HHAR that *does* provide support for statements in current collections of principles. Moreover, such a set of general principles can serve two additional important functions. Such a set of principles can assist in *making the case* for HHAR and various ways it uses animals by indicating more fully how, and why, ethically conducted HHAR includes attention to the interests of animals as well as of humans who benefit from it. Second, such a set of principles can identify what is properly characterized as the *central ethical structure* of HHAR: general principles on which all assessments of the ethical appropriateness of research and animal care practices in HHAR ultimately rest.

The Ethical Core of HHAR

There is I want to suggest a set of sound general principles that is already present in the ethical attitudes of those who are involved in HHAR and that can be regarded as its *ethical core*. This core as I conceive of it does not consist of all general ethical principles, or even all significant general ethical principles, in HHAR. The principles in the core are the most important ethical principles in HHAR. These principles serve as final touchstones for all ethical decision-making in HHAR, because as particular issues are considered, ultimately one and sometimes more than one of the principles in the core will be cited as determinative. Despite their generality, core principles often provide substantial guidance regarding the appropriateness or inappropriateness of research practices and treatment of animals. Core principles sometimes do this directly, and sometimes imply other core or non-core principles that apply to an ethical issue or factual circumstances at hand.

The logical structure of the ethical core enables it to be used to make the case for HHAR and to describe its central ethical structure. At the base of the core are what I shall call *foundational* ethical principles and supporting factual truths on which rest all the other principles in the core. Some of these foundational principles and truths do not refer explicitly to animals or the use of animals in research. From these foundational ethical principles and factual truths, there follow, in light of additional relevant facts, what I shall call (non-foundational) *basic* principles in the ethical core: successively more concrete general principles that explain further the meaning or appropriate applications of the principles from which they follow. Put another way (and as is illustrated below), we begin by stating and defending foundational ethical principles and relevant facts. These principles do—and should—strike the vast majority of people as sound. From these principles, employing important facts relating to humans, animals, and HHAR, we can deduce somewhat more concrete sound general principles. And from these latter sound general principles and additional relevant facts we can deduce additional sound general principles that are still more concrete. This process can be repeated as general principles require clarification or are applied to additional issues. However, at some point in this process, one reaches principles that should not be regarded as part of the ethical core of HHAR. These principles are not sufficiently general, and do not apply to a sufficiently wide range of ethical issues, to be core principles.

Where one draws the line between principles in the core that are so clearly foundational that they should be regarded as the basis of the core, and core principles that are not foundational, may sometimes be open to disagreement. The principles and supporting facts I classify as foundational are the most general, and the least objectionable (at least to the vast majority of people), and from which the process of deducing successively more concrete core principles *begins*. For example, I include in foundational core principles the principle that harming animals in HHAR must be justified, but I do not include principles that indicate what *constitutes* harm and *when* and *why* causing such harm is or is not justified. Drawing the line in this way facilitates identification of core principles that clarify more general principles, and allows the presentation of these clarifying principles to be organized around issues they address.

The ethical core of HHAR is not static, and the substance and precise wording of its principles are open to discussion and debate. As is noted below, it may be possible for a principle (e.g., that research animals should be provided pleasurable experiences) that does not follow from or is not suggested by an existing core principle, to make its way into the core. Such a new principle might reinforce, although for a different reason, some of the existing core and non-core principles; it may also imply new core or non-core principles. As more is learned about techniques of animal research and about research animal welfare, and the concerns and emphases of the research community and the public develop, a principle that already is implied by a current principle in the core but previously might not have been included in the core itself can be added. For example, a principle that has long been in the core is that as expressed in the *US Principles*, "(t)he living conditions of animals should be appropriate for their species and contribute to their health and comfort." (Principle VII) In light of what has been learned about research animal behavior and welfare since the *Principles* were written in 1985, some implications of Principle VII have gained significant prominence in their own right. Thus, the US National Research Council (NRC) *Guide for the Use and Care of Research Animals* (*Guide*), which must like the *US Principles* be applied in animal research funded by the NIH, states that "(a)n appropriate housing space or enclosure should also account for the animals' social needs. Social animals should be housed in stable pairs or groups of compatible individuals unless they must be housed alone for experimental reasons or because of social incompatibility." (NRC, 2011b, p. 51) This statement is universally endorsed in the animal research community, and applies to so many species used in HHAR, that a general requirement of social housing when appropriate clearly belongs in the ethical core. As does, for the same reasons, the obligation to provide, when consistent with justified experimental goals, environmental enrichment, which can be defined as "a combination of complex inanimate and social stimulation and generally consists of housing conditions that facilitate enhanced sensory, cognitive, motor and social stimulation … [and] provides the animals with opportunities to perform some of their species-specific behavioral repertoire." (Sztainberg & Chen, 2010, p. 1535) Some might maintain that if principles addressing social housing and environmental enrichment belong in the core, so do principles relating specifically to other aspects of housing that can affect research animal

welfare and the importance of which is also implied by Principle VII, such as water and air quality, temperature, noise, and facility lighting. In my view these inclusions would be unwise because they might detract from the usefulness of the core in expressing very general principles, but some might disagree.

Even if a principle is implied by the core, but does not fall within it (such as the principle that animals should be provided fresh and clean air), it can still be a principle that HHAR must follow as carefully as any. Indeed, because of the power and broad applicability of general principles in assessing and guiding research activities, the articulation of successively more concrete ethical principles can be extended well beyond the ethical core, to various kinds of HHAR and various species, experimental methods, and ways of housing and caring for animals. Moreover, certain kinds of HHAR employ distinctive research methods and lend themselves to articulation of sets of ethical principles that are so central to these areas that they can be regarded as stating core ethical principles of *these* kinds of HHAR (Tannenbaum, 1999 [pain research]; Tannenbaum, 2017b [studies of epilepsy and seizure disorders]).

Presentation of the Core

The presentation of the ethical core of HHAR that follows first identifies and defends foundational and (non-foundational) basic core ethical principles that are *established* in the sense that they seem clearly correct and any practicable approach to HHAR must regard them as axiomatic. Unsurprisingly, these principles are virtually universally accepted by, or follow logically from principles virtually universally accepted by, the biomedical research community, the general public, and government authorities who regulate HHAR. The discussion also examines general principles that are *potentially emergent* for the ethical core of HHAR in the sense that they may well in the future, in some form, be regarded as belonging in the core. However, at least at present, these principles cannot be included in the core because they raise difficult issues that are as yet unresolved, or because there is not yet sufficient consensus regarding their precise content or underlying justification.

Established Core Ethical Principles and Supporting Facts

Established Foundational Core Principles and Supporting Facts

The entire enterprise of HHAR is motivated and ultimately justified by an incontrovertible fact, F1: *Many human beings suffer from diseases that shorten or end their lives; cause them significant pain, distress, discomfort, disability, fear, and anxiety; cause their families and friends great distress, anxiety, and sorrow; and have significant effects on the economy, by affecting the ability of disease sufferers to earn a*

living and by necessitating personal and societal economic costs to facilitate their health care.

F1 provides the impetus and support for a correspondingly foundational ethical principle, EP1: *It is appropriate—indeed obligatory—for human society to employ scientific research to study human disease, and to expend significant resources when necessary in this endeavor.* EP1 is so widely accepted and so obviously correct that some may think it does not need mentioning. However, consideration of the ethical use of animals in HHAR should explicitly acknowledge this principle and its importance, urgency, and great moral weight. There is little if anything that is more important for society to do than to attempt to prevent, alleviate, and cure human disease. And essential in the understanding of and ability to battle human disease is scientific research.

A corollary of EP1 is EP2: *The more important it is to study a human disease, the greater is the weight of this importance in a determination of the ethical appropriateness of studying the disease.*

Several factual truths and ethical principles lay the foundation for the appropriateness of using *animals* in the study of human disease. The first of these is EP3: *Humans are of greater worth and value than nonhuman animals*. The vast majority of people around the world accept EP3, and for most people, EP3 provides the support for EP4: *It is sometimes ethically appropriate to use animals for human benefit.* One can accept EP4 without accepting EP3. A utilitarian, for example, can argue that although there is nothing morally special about being human, some human uses of animals, including HHAR, are ethically acceptable (indeed obligatory) because these uses result on balance in more total pleasure, happiness or benefits for humans than suffering or detriments to animals (Frey, 1988). However, as a number of opponents of animal research appreciate, typically underlying EP4 is the view that humans are intrinsically more important and valuable than nonhuman animals and that therefore we may sometimes use them for our benefit. This is why opponents of using animals for human benefit (including in HHAR) argue that humans are not in virtue of being human of greater worth and value than nonhuman animal species (e.g., Cavalieri, 2002; Francione, 2009; Regan, 1983).

HHAR would be at best pointless and at worst ethically questionable were it not for another incontrovertible fact, F2: *The use of animals in scientific research can be an effective and indispensable tool in the study of human disease.* Critics of HHAR have claimed among other things that there is insufficient evidence that animal research has resulted in net benefits to humans (DeGrazia & Sebo, 2015; Rowan, 2012; Singer, 1975); that using animals to study human disease may have been valuable in the past but is being replaced by new scientific tools and techniques such as computer modeling and studies on humans (HSUS, 2021); and that animal research causes great harm to humans because it diverts resources from scientific research that, unlike animal experimentation, can advance the study of human disease (Akhtar, 2015; Greek & Greek, 2000). It is beyond the scope of this chapter to address such claims in detail. As is noted below, there is widespread agreement among animal researchers that more must be done to identify kinds of studies that are likely to contribute to the understanding of disease, and that more can be done

to improve scientific rigor, transparency, and reproducibility in HHAR. Nevertheless, it is absolutely clear that animal research has made essential contributions to the prevention, alleviation, and cure of many serious human diseases, and is likely to continue to do so for the foreseeable future (Botting & Morrison, 1997; Friedman et al., 2017; Gay, 1984; Genzel et al., 2020; IOM, 1991; Kinter et al., 2021; Kiple & Ornelas, 2001; Maurer & Quimby, 2015; Merrill, 1986; Phillips & Westerfield, 2014; Phillips et al., 2014; Quimby, 1998; Walsh et al., 2017; Warfield & Gay, 1984).

The foregoing factual truths and ethical principles support the principle that is the ethical foundation of HHAR, EP5: *It is sometimes ethically appropriate to use animals in scientific research to study human disease.* If it is sometimes ethically appropriate to use animals to benefit humans it must sometimes be appropriate to use animals in a way that will further arguably the most important of human benefits—the prevention, alleviation, and cure of human diseases that cause countless people pain and suffering, disability, misery, and death.

A corollary of EP4 and EP5 is EP6: *When scientifically and ethically appropriate, the study of a human disease should be conducted in animals before it is conducted in humans.* This principle is reflected in the provision of the post-World War II Nuremberg Code that medical research on human subjects "should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment." (Nuremberg Code, 1947, para. 3) EP6 does not imply that any animal species may be used to study any human disease. EP6 allows precluding the use of certain species (e.g., chimpanzees) to study any or certain diseases and requiring greater justification for the use of some species to study some diseases. As is discussed below, there is reasonable disagreement about the ethical significance in HHAR of species membership. In order not to foreclose such disagreement, EP6 holds that while investigators should generally attempt to first employ animals in HHAR, use of a given species in a given way must be not only scientifically but also ethically appropriate.

The broadest foundational core ethical principle relating to how animals are used and treated in any HHAR project is EP7: *There must be sufficient ethical justification for anything that is done to animals and for anything animals undergo or experience in an HHAR project.* Some readers may regard this principle as superfluous because it might appear simply to restate the general concern of animal research ethics, namely whether animal experiments or kinds of experiments are justified. However, EP7 as presented here can play a distinctive role in ethical assessment of HHAR. The great majority of discussions of the ethical appropriateness of animal research in general and of HHAR in particular focuses on the issue of whether any *harm* done to animals is justified. However, as is discussed further below, there is disagreement regarding what constitutes such harm. Many, but by no means all, researchers and commentators believe that most things that are done to animals in HHAR—including confining them in cages, preventing them from exhibiting all their natural species behavior, and killing them—do not in themselves constitute harm. In order not to foreclose relevant ethical discussion, it is important to

postulate that such things, and indeed anything done to or with the animals must be justified, whether or not these things should be regarded as harm or causing harm.

Because so much of current ethical discussion of HHAR focuses on whether and when this research causes harm to animals, it is important to recognize the presence in the ethical core of HHAR of the following two general (and self-evident) principles:

EP8: *Harm is an evil to something that can be harmed.*
EP9: *One must therefore have sufficient justification intentionally to cause it harm.*
From EP8 and EP9 follows EP10: *An HHAR project must not cause harm to animals without sufficient justification.*

Some readers familiar with the animal research ethics literature may be puzzled by use in EP10 (and EP11 and EP12 below) of the words "harm" instead of "pain or distress" and "justification" instead of "benefit to humans." Discussions in animal research ethics typically begin with the question whether the *likely benefits*—taken to mean probable effective medical treatments or approaches to human disease—justify any *pain or distress or other significantly unpleasant sensations or feelings* experienced by the animals. This is in my view a major mistake that limits ethical discussion. Although pain and distress and other significantly unpleasant experiences are harms to research animals when they occur, it should at least be open to debate whether they are the only harms that can be caused to these animals. Moreover, as is discussed below, it is unreasonable to limit justifications of HHAR to likely medical benefits. It is more helpful to phrase *foundational* core principles in terms of the more generic "harm" and "justification"—and then to identify ethical principles and supporting facts that address the issues of what more precisely constitutes harm and might justify its causation.

From EP8, EP9, and EP10 follow two additional foundational core principles:

EP11: *The greater the harm an HHAR project causes animals, the stronger must be the justification for causing this harm.*
EP12: *When an HHAR project is justified in using animals in any way that has the potential of causing them harm, the project must whenever possible prevent the occurrence of such harm, eliminate this harm if and when it occurs, and minimize this harm if and when in light of experimental aims it must occur.* Because harm to animals ought not to be caused without sufficient justification, any harm that is not necessary for, or an unavoidable consequence of, justified experimental aims and that can be prevented, eliminated, or lessened, is unjustified. It is important to acknowledge that EP10 cannot function independently of EP8 as a justification of an HHAR project, experimental technique, or way of using or caring for research animals. That a project or some aspect of a project causes minimized harm to the animals does not imply that this minimized harm is justified. There must be sufficient ethical reason to cause this minimized harm. It is conceivable that some project or aspect of some project that causes animals minimized harm would inflict sufficient harm, or a kind of harm, that is unacceptable.

Established Basic Core Principles and Supporting Facts

Animal Harm and Its Justification in HHAR

Basic (nonfoundational) core HHAR ethical principles as I understand them follow from and clarify foundational core principles. Because so much of current discussion of the ethics of HHAR, and many of the foundational core ethical principles identified above, center around harm to research animals, it is reasonable to focus deduction of basic core principles on principles that address the nature and justification of such harm.

Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings as Harm

Whatever else might be included in the definition of "harm," there is universal support by all who conduct or engage in ethical assessment of HHAR (and other kinds of animal research) of a factual truth that has an evaluative component and therefore can also be classified as an ethical principle, EP13: *Pain, distress, and other significantly unpleasant feelings or sensations are harms or evils to animals when experienced by them, just as they are harms or evils to humans who experience them.*

There is also universal support of an incontrovertible fact, F3: *Most species used in HHAR are capable of feeling pain, distress, and other significantly unpleasant sensations or feelings, as independent experiences or as part of more complex emotions such as fear, anxiety, or boredom.* A great deal of scientific research has been conducted on understanding pain and distress in animals in general and research animals in particular (Carstens & Moberg, 2000; NRC, 2008, 2009). It may not be clear whether all species employed in HHAR can experience certain unpleasant sensations or feelings, or complex unpleasant emotions. It may not always be clear how various aspects of unpleasant experiences should count in quantifying their unpleasantness, for example, whether a long period of moderate distress should be regarded as equivalent in unpleasantness to a brief period of severe pain. Although much is known, much more remains to be learned about how unpleasant experiences in research animals can be prevented or minimized. However, it is clear that many animals used in HHAR can—and some sometimes do—experience painful or unpleasant sensations and feelings that, if not identical to those experienced by humans, can often be as painful or unpleasant. The best source of data in the US regarding research animal pain and distress are annual reports of facilities registered under the AWA by the USDA. According to the latest data as of the time of this writing, in fiscal year 2019, of the 797,546 animals used in AWA-regulated research (USDA, 2021c), 225,404, or approximately 28%, were used in procedures (such as surgeries) that could be painful or distressful but in which pain or distress was prevented by use of appropriate anesthetic, analgesic, or tranquilizing drugs (USDA, 2021a); and 49,422, or approximately 6%, experienced some unrelieved pain or distress (USDA, 2021b). (AWA reports do not

distinguish between HHAR and other kinds of animal research.) As noted above, the AWA does not cover and therefore does not ask for the counting of the number of mice and rats that experience pain or distress. However, there is no *a priori* reason to suppose that a higher percentage of these species experience pain or distress than do AWA-covered animals. Nor is there reason to suppose that a higher percentage of animals used in HHAR experience more pain or distress than do animals in other kinds of research. Nor is there reason to suppose that research animals used in the US experience more, or less, pain or distress than do animals in other countries that engage in serious legal regulation of animal research. Therefore, whether the number of animals used annually in research in the US is ten million, or 100 million, or somewhere in between (see f.n. 2 above), the number used in the US and other countries in HHAR that experience some unrelieved pain or distress is not insignificant.

Justification of Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings

EP13 and F3 support the presence in the HHAR ethical core of the following two principles, which are more concrete applications of foundational core principles EP10 and EP11.

EP14: *Animals must not be caused pain, distress, or other significantly unpleasant sensations or feelings in an HHAR project without sufficient justification.*

EP15: *The greater the pain, distress, or other significantly unpleasant sensations or feelings animals are caused in an HHAR project, the stronger must be the justification for causing these experiences.*

The process of determining whether an HHAR project justifies any pain or other significantly unpleasant experiences it may cause animals is often called "balancing" or "weighing" the value of the project against the unpleasant experiences. This language is entirely metaphorical and does not identify considerations relevant to making this determination. These metaphors might suggest to some that the determination is utilitarian in nature, i.e., that an HHAR experiment is justified if and only if it will result on balance in more total benefits to all humans than pain and distress to animals used in the experiment. However, as is discussed below, the value of HHAR experiments that can justify using, and sometimes harming, animals cannot be identified with their resulting in benefits such as the prevention, alleviation or cure of disease. Moreover, the demand of utilitarians like Singer (1975) to the contrary notwithstanding, humans and research animals are not commonly viewed as equals whose pains and pleasures count equally. It is possible that an experiment that causes distress to a large number of mice, for example, and would help a relatively small number of humans with a moderately discomforting ailment would seem justified—even if the total distress suffered by the mice exceeds the

benefits to the humans. An experiment that would cause excruciating long-lasting unrelieved pain and suffering to relatively few cats, but would benefit a large number of humans who have a disease for which there are already reasonably effective treatments would likely seem unjustified—even though the total pain suffered by the cats would be exceeded by the benefits to the humans. To be sure, when it contributes to medical advances, HHAR almost always results in benefits to *very* large numbers of humans at the expense of far fewer animals. However, for the vast majority of people, determining whether the value of an HHAR project justifies any harms it might cause animals is not simply a utilitarian exercise but rather a consideration of whether, when a wide range of *varied* factors are taken into account, what is done to the animals is justified.

Importance of Studying the Disease

In determining whether an HHAR experiment that might cause animals pain, distress, or other significantly unpleasant experiences—or any other kind of harm—is justified, one clearly relevant consideration is the seriousness of the disease the experiment studies and the importance of discovering a prevention, amelioration, or cure of the disease. There are numerous factors that can be relevant to determining the importance of studying a given disease including: the number of people who have the disease; whether or to what extent the disease is life-threatening or fatal; the nature and extent of pain and distress or other significantly unpleasant sensations or feelings associated with the disease; whether, to what extent, and how the disease is transmissible to others; whether there are current effective treatments of the disease; the risks or side-effects of current treatments; whether and to what extent the disease is caused by choices in behavior or lifestyle; the economic cost to patients of available treatments; the extent to which the disease imposes financial costs on the health care system or the general economy; and whether studying the disease may contribute to understanding similar or other diseases. Often some of these (and other) relevant factors must be considered concurrently, and must be weighed against each other. This can make it difficult to assess the importance or comparative importance of studying a disease.

Scientific Soundne of the Study

That an experiment studies a disease it is important to combat does not however imply that the experiment has great value and justifies animal pain or distress or other harms. If the experiment seeks to answer questions that have no scientific merit, or addresses sound questions with poorly designed or executed methods, or is conducted by investigators who are unqualified or do not have adequate facilities and equipment to apply sound scientific methods to sound questions, the experiment

will not be valuable from a scientific standpoint.[4] It will not discover knowledge useful in understanding the disease. *Any* pain or distress or other harm it causes animals cannot be justified by its relevance to the study of human disease.

One of the most significant recent developments relating to the ethical conduct of HHAR have been measures taken in the animal research community to improve the scientific soundness of animal experiments (e.g., ACD, 2021; AMS, 2015; Cheleuitte-Nieves & Lipman, 2022; Festing, 2020; Macleod & Mohan, 2019; NASEM, 2020). These efforts acknowledge and are motivated by the recognition that some scientists in HHAR have not engaged in best research practices that enable their work to be reproduced or assessed by others. This has resulted in experiments that do not advance the study of human disease and thus can subject animals to pain and distress that is not ethically justified because it is not scientifically justified. Efforts to improve the scientific rigor, transparency, and reproducibility of HHAR projects include recommendations of inclusion of statisticians in the design and institutional assessment of experiments; greater attention to determination of adequate sample sizes; minimization of risk of investigator bias through use of sample randomization methods; improved knowledge and education of investigators regarding which kinds of animal models and studies have been or are more likely to be translatable to clinical medical advances; greater understanding of and attention to effects on experimental results of environmental conditions of animal housing and care; and use by investigators of standardized guidelines for planning, conducting, and reporting experiments that enable others to assess and when scientifically appropriate to reproduce experimental results. Among innovative suggestions for promoting scientific soundness of animal experiments have been proposals for researchers to register their experimental designs and results in a confidential repository that would allow for subsequent comparison of actual with intended or predicted results, and methods of reporting negative results that could prevent other investigators from conducting the same or similar unpromising experiments. Two sets of rules for planning, conducting, and reporting animal experiments that enhance scientific rigor, transparency, and reproducibility, the ARRIVE (Percie du Sert et al., 2020) and PREPARE (Smith et al., 2018) guidelines, are already widely used by animal researchers.

[4] Assessment of the scientific soundness of experiments is a difficult and complex task and is beyond the scope of this chapter to consider in detail. There are undoubtedly different reasonable approaches. The NIH, for example, asks reviewers of proposed projects seeking funding to appraise and score five primary factors: significance, investigator(s), innovation, approach, and environment. "Significance" and "innovation" relate to the quality of a project's scientific aims and design and its potential contributions to the understanding of an important disease; and "approach," "investigator(s)," and "environment" to the likelihood it will fulfill its goals (NIH, 2016a, 2018).

Likelihood of a Valuable Result

From EP10, EP11, EP14, and EP15 it follows that if an HHAR experiment does cause animals pain or distress, there ought if possible to be *something* of value that the experiment might discover that is sufficient to justify this pain or distress. Some argue that an HHAR project cannot justify causing animal pain or distress unless it is *highly likely* that the project *will* result in *medical benefits* for humans that outweigh the pain and distress (Rollin, 1992, p. 140). Proponents of this view commonly call "harm-benefit analysis" the process of determining how much pain or distress or other harms a proposed experiment will cause animals, what benefits it might produce for humans, how likely it will be to produce such benefits, and whether this likelihood of these benefits justifies the pain or distress or harms (AAALAC, 2020; Brønstad et al., 2016; Laber et al., 2016).

Several discussions demonstrate in detail why such harm-benefit analysis can be profoundly anti-scientific and indeed dangerous (Grimm et al., 2017; Niemi, 2020; Tannenbaum, 2017a). It is sufficient here to note briefly some of its problems. First, as is reflected in the NIH Mission Statement (NIH, 2017) quoted above, a great deal of biomedical experimentation is fundamental or basic, in the sense that it seeks to understand foundational, underlying mechanisms or causes that it is hoped might eventually explain a wide range of phenomena. Such research typically does not expect to quickly make discoveries with specific relevance to practical results, precisely because the research seeks to find causes and explanations of matters that are not yet well understood. Even when it is hoped that basic research will result in medical benefits, such results usually cannot be predicted, because typically it will not be clear how the findings of the research can impact human health until additional research is done or until investigators can determine how this and additional research can be applied to particular diseases. This can take years, sometimes decades, and must sometimes await future discovery of entirely new and sometimes unexpected or unpredictable knowledge or technologies (Comroe & Dripps, 1976). Second, it almost always cannot be known before an experiment is completed precisely what its results will be; if things were otherwise, it would not be necessary to conduct the experiment. Third, failure is an important element of the scientific method; that an experiment does not discover anything, or determines that a proposed hypothesis or prediction is incorrect, can be valuable because it can advance basic or clinical research by channeling experimentation in other directions.

Requiring all HHAR projects that harm animals to promise likely medical benefits would stifle the discovery of knowledge necessary for future medical benefits. To be sure, if an HHAR project *is* likely to result in significant benefits, this would count heavily in justifying its causing a proportionate amount of pain or distress or other harm in animals. It is therefore appropriate for investigators and those who oversee their work to ask about the potential for practical medical benefits of HHAR projects. However, likelihood of benefits cannot be a necessary condition for the justification of all projects.

It is reasonable, in assessing the value of an HHAR project that might harm animals, to consider its likelihood of producing *some* valuable scientific result. Whether

an experiment seeks to produce such a result, and how likely it is to produce such a result, are matters for scientists familiar with the area under study to assess. When it is unclear before an HHAR project is conducted what, if any, scientifically valuable knowledge it will discover, it will likely be the importance of studying a disease and the soundness of the science of the experiment that determines whether and to what extent the experiment may appropriately cause animals pain or distress. If, for example, an experiment that is scientifically sound will study a disease of great importance about which much remains to be learned, it may be reasonable to take the chance that something of value will be discovered—even if taking this chance might involve some animal pain or distress.

The foregoing considerations are summarized in core ethical principle EP16: *Contributing to the value of an HHAR project to be weighed against any pain, distress, or other significantly unpleasant sensations or feelings—or any other kind of harm—it might cause animals are (1) the importance of understanding and combatting the disease or diseases under study and of any means of prevention, amelioration, or cure that the project might seek to discover; (2) the scientific soundness of the project and the capacity of the investigators to undertake it properly; and (3) the possibility or likelihood that the project will achieve a valuable scientific result.*

It is far easier to identify ethical principles that seek to ensure the appropriateness of research techniques and housing conditions in ongoing or clearly justified HHAR projects, than to formulate sound rules that can assist in determining when projects are justified in the first place. (This might explain why, as noted above, the *US Principles* focus on the former and say very little about the latter.) Much work is needed to clarify further each of the three considerations in EP16, how heavily each should count in favor or against given HHAR projects or kinds of HHAR, and how they should be balanced against each other in determinations of the appropriateness of causing animals pain, distress, or other harms. Serious and sustained consideration of these matters may result in identification of principles that follow from EP16 and belong in the ethical core of HHAR.

Minimization of Pain, Distress, and Other Significantly Unpleasant Sensations and Feelings

From EP12 and EP13 follows what I call above the pain and distress minimization principle, EP17: *When an HHAR project is justified in using animals in any way that has the potential of causing them pain, distress, or other significantly unpleasant sensations or feelings, the project should prevent the occurrence of such sensations or feelings if possible, eliminate them if and when they occur, or minimize them if and when in light of justified experimental aims they must occur.*

As is emphasized above regarding EP11 and causing harm to research animals generally, that some aspect of an HHAR project causes pain or distress that is minimized does not imply that this pain or distress is justified. There must be sufficient ethical reason to cause this minimized pain or distress.

In their 1959 groundbreaking book, *The Principles of Humane Experimental Technique*, Russell and Burch articulated what has become the most commonly cited principle in ethical discussions relating to HHAR and animal research generally. Russell and Burch recommended that investigators employ what they termed "the 3Rs," three general ways of eliminating or minimizing pain, distress, fear, and other significantly unpleasant experiences in experimental animals.

> Replacement, Reduction, and Refinement. … Replacement means the substitution for conscious living higher animals of insentient material. Reduction means reduction in the numbers of animals used to obtain information of a given amount and precision. Refinement means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used. (Russell & Burch, 1959, p. 64)

Although citations to Russell and Burch are omnipresent in ethical discussions of HHAR, the 3Rs as they understood them are often misinterpreted (Tannenbaum & Bennett, 2015). Russell and Burch made clear that the *sole* aim of all 3Rs is the prevention, elimination, or minimization of pain and other significantly unpleasant experiences. (They termed "inhumane" any experimental procedure that causes animals unrelieved pain, distress, fear or other significantly unpleasant sensations or feelings. This term was not intended to express disapproval of all such procedures, but to emphasize that these procedures harm animals and should whenever consistent with experimental aims be avoided.) Although replacement and reduction are means of attaining this end, "refinement" for Russell and Burch refers to the broad range of techniques that address the minimization of these experiences directly. They had no problem with the use of animals in research and did not regard their use as a necessary evil that replacement or reduction function to mitigate. They did not, contrary to the opinion of many, define "replacement" as not using animals. By "replacement" they meant not using animals that can have unpleasant experiences during experimentation. Thus, employing completely anesthetized animals (a common practice in HHAR) is a form of replacement. Russell and Burch viewed reduction of the number of animals used in experiments as a way of causing less pain, distress, fear, or other significantly unpleasant experiences. However, they also emphasized that using too *few* animals could render an experiment scientifically unsound and result in unnecessary and therefore unjustified pain and distress (Tannenbaum & Bennett, 2015).

The 3Rs as understood by Russell and Burch are concrete applications of EP17. They clearly belong in the ethical core of HHAR and are designated here as EP18: *In preventing, eliminating, or minimizing pain, distress, or other significantly unpleasant experiences in research animals, investigators should employ replacement, reduction, and refinement as defined by Russell and Burch in The Principles of Humane Experimental Technique.*

EP14, EP15, EP16, and EP17 provide support for another established core ethical principle in HHAR, EP19, stated here in the language of the *US Principles*: *"The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered."* (US Principles, 1985, Principle III) If the species used in an

experiment is not appropriate for addressing questions the experiment asks, or the animals employed do not have characteristics that are useful in addressing these questions, the experiment will not be scientifically sound and any pain or distress the animals experience will be unnecessary and wrong. If more animals are used than is required for scientific reasons, and if these unnecessary animals experience pain or distress, there will be more pain or distress than is scientifically and therefore ethically justified. And if a project or part of a project, can be accomplished without using animals, the project or part of it will not cause any animal pain or distress.

The following established core principles of HHAR also follow from EP17, the pain and distress minimization principle. When applicable, language quoted from the *US Principles* is employed in stating these principles because of the widespread use, and in the US the legal status, of this document.

EP20: *"Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents."* (US Principles, 1985, Principle V)

EP21: *"Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure."* (US Principles, 1985, Principle VI)

EP22*: Procedures should include humane endpoints that prevent animals from experiencing unrelieved pain or distress that is not necessary for, or an unavoidable consequence of, achieving experimental aims.*

Methods of effecting such endpoints can include terminating a procedure before onset of pain or distress if experimental aims have been achieved; euthanasia of moribund animals that are not required by a procedure to remain alive; and euthanasia of animals that are not required to remain alive but will become moribund or will survive the procedure with significant illness or disability (Stokes, 2000).

EP23: *"The living conditions of animals should be appropriate for their species and contribute to their health and comfort."* (US Principles, 1985, Principle VII) *When consistent with experimental aims and individual animal health and welfare, social animals should be housed in species-appropriate pairs or groups and should be provided environmental enrichment that promotes species-typical behavior.*

EP24: "*Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.*" (US Principles, 1985, Principle VII)

EP25: "*Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.*" (US Principles, 1985, Principle VIII)

EP26: *In all stages of a project, and in all aspects of animal housing and care, all who handle, interact with, or affect animals shall do so as carefully and gently as possible, in accordance with species-specific and individual behavior and needs.* This principle applies not just to those who touch, move, or physically administer medicine or other care to animals in a housing facility, but also to those who are in the facility to observe animals or to maintain the cleanliness and general environmental conditions of the facility. The principle requires among other things avoiding making noise and causing vibrations that can result in animal distress or discomfort (NRC, 2011b, pp. 49–50).

Justification of Debatably Harmful or Nonharmful Practices

Although core ethical principles of HHAR require the justification and minimization of harm to research animals, there is some disagreement about whether certain common practices in HHAR harm these animals.

Killing Research Animals

For some time, the prevalent view in the animal research community has been that merely killing animals (i.e., killing without causing pain, distress, discomfort, or other unpleasant sensations or feelings) does not *harm* them because, it is claimed, they do not have a concept of life and a desire to live, or a concept or a fear of death (e.g., Cigman, 1981, pp. 53–59; Webster, 1994, p. 15). Others argue that even a painless death is a misfortune and harm for animals because it prevents them from having, and potentially enjoying, a future life (e.g., Harman, 2011; Regan, 1983, pp. 99–103). Although this is an interesting dispute, its resolution is not necessary to establish the ethical acceptability of killing research animals in appropriate circumstances. EP7 requires generally that there must be sufficient justification for *anything* that is done to animals in an HHAR project, whether or not it is characterized as harm or causing harm. Sometimes, indeed often, animals must be killed so that, at some stage in an experiment, or at its conclusion, their bodies, tissues, or cells can be examined. Sometimes they must be killed because this is the only way to prevent their experiencing pain or distress. Sometimes they must be killed because, due to disease, infirmity, or unsuitability for a study they cannot be used further.

The claim that killing animals in HHAR is wrong in itself simply is unlikely to be accepted by the vast majority of people. It is impossible for a society to accept killing animals to produce meat for human consumption (which many people enjoy but almost all could survive without) and reject killing animals in research that seeks to allow many people to live and enjoy the pleasures of life (including the eating of meat). Indeed, in light of the insignificance of the gustatory pleasures of meat-eating relative to the importance of conquering disease, an HHAR project is

likely to appear justified in killing animals even if it might add just a *small* amount of knowledge to the understanding of an important disease. The great majority of animals used in HHAR are either kinds of animals that already are killed and eaten by many people (such as pigs, rabbits, sheep, and fish) or are considered by many people of even lesser value and unfit for human consumption (such as mice, rats, and other rodents). As is discussed below, there is debate regarding whether certain species used in HHAR are of such high value that killing them (whether or not classified as harm) requires special or weighty justification, or is sometimes unacceptable. EP7 is sufficiently broad to allow for such debates, and for additional core or non-core ethical principles relating to killing or certain uses of these species.

Caging or Confinement

Some philosophers and animal welfare advocates argue that the inborn nature or to use the Aristotelian term "*telos*" of animals must be respected by people who use them for their own benefit (Rollin, 1992). According to this view, merely caging or confining animals, even in the absence of resulting unpleasant experiences, harms them because they are not allowed to behave in ways normal for their species. Among the problems with this view is that animals in their natural state frequently experience hunger, injury, pain, distress, predation, and painful death, which do not occur in the protected confines of research facility animal housing. It is also unclear why the promotion of *telos* is in itself obligatory, in light of the fact that much of modern medicine seeks to counter some of humans' natural, inborn tendencies, including our programmed nature to grow old and infirm and die. Laboratory HHAR projects require caging or confining animals so that they can be kept in appropriate numbers and conditions for research. It is conceivable that an HHAR project would require for scientific reasons the housing of animals in a way that would so interfere with their natural behavior that it would render the project unethical. However, aside from the fact that it would likely be the pain and distress these animals would experience that would invalidate the project, EP7 is sufficiently broad to enable taking into account the housing conditions of laboratory animals in determining a project's appropriateness, even if merely caging or confining the animals could count to some extent against it.

Potentially Emergent Core Ethical Principles

Potentially emergent core ethical principles as I understand them seem at least in part reasonable and correct and at some time may well be universally regarded as belonging in the ethical core of HHAR. However, these principles raise difficult or contentious issues that are as yet unresolved, or lack the consensus in the research community and general public necessary for inclusion in the core.

Adoption of Healthy Animals: Possible Core Justifications

Some investigators and HHAR facilities attempt to place with private owners or animal adoption agencies animals that are no longer needed in experiments and are sufficiently healthy and well-behaved to be kept as pets (Carbone et al., 2003). A number of US states have enacted laws that require research institutions to facilitate adoption of such animals, specifically cats and dogs (e.g., California, 2015; Nevada, 2015; Oregon, 2019; Virginia, 2021). The American College of Laboratory Animal Medicine (ACLAM), the body that certifies veterinary specialists in this field, states that it "fully supports the concept of adoption of healthy, post-study, research animals into long-term, caring private homes or farms that can provide appropriate and humane living conditions for these animals as pets." (ACLAM, 2017) It is fair to say that many researchers agree, provided animals are not removed prematurely from studies for the purpose of adoption. It is not clear whether ACLAM, laboratory animal veterinarians, or investigators believe that they are ethically *obligated* to try to place suitable healthy animals for adoption, or that this is an admirable practice that is an ideal and not an ethical requirement. It is also unknown at the time of this writing how many former research animals are adopted and how significant this practice is or is likely to become.

Even if one believes that HHAR investigators and facilities *are* ethically obligated to make suitable animals, at least cats and dogs, available to suitable new owners, it is unclear that a principle specifically requiring, or even just recommending, adoption belongs in the ethical core of HHAR. First, because the great majority of research animals are *not* alive or suitable for adoption at the conclusion of studies, it is doubtful that, unlike other research and animal care practices addressed directly in the core, placing animals for adoption is or will constitute a large proportion of the activities of investigators or facilities. Second, a principle relating to this practice requires a more general principle that supports it; it cannot simply be asserted as self-evidently correct. However, there is nothing in the ethical core of HHAR as thus far presented that supports an adoption requirement or recommendation. A requirement would not follow from the obligation to minimize pain, distress, or other significantly unpleasant experiences; one could accomplish this by euthanizing healthy animals no longer needed in studies.

There are several candidates for core principles that would support an appropriately worded adoption principle. One could identify in the core a principle that asserts that animal life is of value and that animals therefore should not be killed without sufficient reason. Most people surely agree that it is wrong to kill an animal if there is no good reason to do so (although they might disagree about what constitutes a good reason). Such a principle if stated appropriately would allow the current practice of euthanizing animals during or at the end of experiments when required for scientific reasons. A second possibility for a core principle that would support adoption would be the principle that when possible research animals should be provided pleasures or happiness in addition to freedom from unnecessary pain or distress. Such a principle would support adoption of healthy research animals on the

grounds that adoption could provide these animals pleasurable experiences. However, a requirement of such experiences raises serious issues, some of which are discussed in the next section. A third candidate for a core principle that many people would probably accept and that supports adoption, would be that investigators should be grateful for the contributions of research animals and thus should when possible give something back to them in return for their (albeit non-voluntary) service. This principle is not yet expressed universally in the animal research community. However, it seems defensible, if stated in a manner that would not compromise the ability of researchers to conduct scientifically sound and ethically justified projects. Such a principle would justify more than making animals available for adoption. A principle expressing gratitude to research animals would also provide justification, in addition to the obligation to minimize pain and other significantly unpleasant experiences, for EP23 through EP26.

Providing Pleasurable Experiences

As discussed above, many of the principles in the ethical core of HHAR relate to the justification and minimization of pain, distress, and other significantly unpleasant sensations and feelings in research animals. There has been emerging in the research community the view that these animals are also entitled to positive experiences—and not just because such experiences can prevent or lessen negative, unpleasant experiences. The NRC *Guide* repeatedly calls for research practices and animal housing that enhance animal "well-being," in addition to freedom from pain or distress. Indeed, it defines "refinement," which Russell and Burch regarded as a tool for minimizing negative experiences, as "modifications of husbandry or experimental procedures to enhance animal well-being *and* minimize or eliminate pain and distress" (NRC, 2011b, p. 5, italics added). The *Guide* also identifies as a goal of environmental enrichment not just preventing "abnormal brain development, physiologic dysfunction, and behavioral disorders," (p. 51), but also enhancing "animal well-being" and "psychological well-being." (p. 52) "Well-being" would appear to include sensations or feelings of satisfaction, contentment, and perhaps various pleasures. Rollin maintains that "all animals kept in confinement for human benefit" should be provided environments conducive to their psychological well-being and that the research community must "begin to seek animal-friendly housing, care, and husbandry systems that allow the animals to live *happy lives* while being employed for human benefit." (Rollin & Kesel, 1995, Preface, n.p., italics added).

It might seem obvious to some that it is more than ungenerous, that it is *wrong*, for researchers not to provide animals positive experiences as well as freedom from negative ones. However, as I have discussed in detail (Tannenbaum, 2002), serious issues must be addressed before an obligation to provide positive experiences is included in the core ethical principles of HHAR. It is not at all clear how terms like "satisfaction," "contentment," "pleasure," or "happiness" should be defined as applied to all species used in HHAR; whether and to what extent we can determine

that these species experience these mental states under various conditions of experimentation and housing; whether requiring pleasures or happy lives for research animals, assuming we know what this means and how to provide it, would hinder or preclude valuable research by greatly increasing its economic cost; and whether, if providing a "happy life" or even more limited pleasures for *all* research animals is obligatory, any experiment that must cause some unrelieved pain or distress, or is not consistent with animal happiness, might be unethical.

Including an obligation to provide positive experiences in the ethical core of HHAR would also likely require changes in the wording or interpretation of some current core principles, and would probably also require new core principles that could have significant implications. For example, if positive experiences are required in their own right, changes might need to be made to the statement of Principle VII of the *US Principles*, and EP18, that "*the living conditions of animals should be appropriate for their species and contribute to their health and comfort.*" "Comfort" connotes an important but nonetheless minimal mental state that would surely often prevent or alleviate distress if not also pain, but need not include greatly positive experiences such as pleasures or happiness. If living conditions must also provide pleasures, or certain pleasures, happiness, or a generally "happy life," more than is now provided to animals may be required. Perhaps not a great deal more, and perhaps not enough to preclude or affect scientifically valuable experiments. But until this and other possible implications of requiring certain positive experiences are investigated and considered, including in the ethical core of HHAR an obligation to provide positive experiences, or some kinds of positive experiences, could be extremely risky.

Stronger Justification for Use of Certain Species

Many animal researchers and members of the public appear to believe that it is preferable to conduct HHAR on some species than others. Mice and rats are favored animals in HHAR not just because many can be genetically engineered for desired traits (including possession of certain human diseases) and bred quickly in large numbers, but also because the public seems to have far less difficulty with experiments on these species than, for example, on cats or dogs (Ipsos MORI, 2018, p. 25). Researchers and those who oversee or regulate their work commonly ask whether experiments that propose to use dogs can be conducted instead on pigs. Most people are likely not bothered about experimentation on fish and frogs. For some people, certain species are either completely off-limits, or must be shown to be absolutely necessary for important medical advances. In 2016, the NIH decided no longer to fund new projects or renewals or revisions of ongoing projects involving chimpanzees, with the exception of projects involving non-invasive research such as "visual observation," and "collections of biological materials (e.g., saliva, oral or other cavity specimens, urine, feces, or hair) obtained voluntarily from a chimpanzee that has been trained through positive reinforcement to cooperate in the

collection." (NIH, 2016b) The NIH decision came after a 2011 report of a committee to study the necessity of the use of chimpanzees in biomedical and behavioral research appointed by the NRC Institute of Medicine (IOM). The committee recommended (NRC, 2011a) that chimpanzees be used only if the "knowledge gained is necessary to advance the public's health" and only if there is "no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects." (p. 4) The committee also stated that "imposing requirements for justifying the use of higher species is an implicit recognition that use of higher animals comes at higher moral costs." (p. 15).

I have called the belief that it is preferable to use some species rather than others in animal research "the relative moral cost view" (Tannenbaum, 2017a, p. 40). This view does not imply that pain and distress are less important to minimize and justify in certain species than in others. Nor does the relative moral cost view involve the reasonable claim that because of their mental capacity some species (e.g., nonhuman primates) may be capable of experiencing more pain or distress than other species, and research causing pain and distress in these animals may therefore sometimes require a higher value of experiments to justify this greater pain or distress. The relative moral cost view holds that a stronger justification—that is, greater value of a research project—is required simply to use or kill certain species, even if the research causes these animals no pain or distress. The relative moral cost view also holds that if it is necessary to cause animals a given amount of pain or distress, it is preferable to do this in some species rather than others.

The relative moral cost view raises difficult questions. If species are to be ranked, persuasive and consistent criteria are needed for ranking. There are a number of possibilities. For example, in speaking of "higher animals," the IOM report appears to suggest that the criteria to be used in ranking species relate to characteristics such as mental sophistication and complex emotions. These criteria may distinguish nonhuman primates from some other animals, but may not do justice to all discriminations many people seem to want to make. Doubtlessly many people think a stronger showing of the value of a research project must be made for using and killing dogs than pigs. What seems to distinguish pigs from dogs is not that dogs are "higher" animals, but that in many countries dogs are beloved pets and pigs are food. A number of criteria can be suggested for distinguishing among species in ways that support demanding a stronger showing of the value of research in using certain species, including whether animals exhibit self-awareness; their mental complexity; the complexity of their natural social behavior; and whether members of their species interact and bond emotionally with human beings (Tannenbaum & Rowan, 1985). These criteria support the widely-held view that using monkeys, cats, and dogs, for example, requires a stronger justification than using mice or rats. However, it is not clear how the cultural and historical preference for dogs over pigs would *justify* requiring a higher value of research for one of two species with comparable mental and behavioral capacities. Moreover, human attachment to dogs and cats would not account for special treatment for nonhuman primates, with which few people interact. If mental sophistication, human attachment, and other considerations are all relevant in determining the moral cost of using these and other species in research,

standards are needed for determining how much weight and relative weight these considerations should be given.

Second, if species are to be ranked, it must also be decided how many categories of ranking should be employed. It can be argued that if it makes scientific and ethical sense to rank species for the purpose of justifying their use, we should *separately* rank all species used in research. This might involve placing species separately along a spectrum, presumably with chimpanzees at the high end, and amphibians and fish, for example, far down the scale. One might then assign a different level of moral cost to research use of each species, and require a stronger justification for use the closer a species is located toward the chimpanzee end of the spectrum. As a demonstration of the difficulty of such ranking—and the possibility of disagreements among researchers and members of the public about where to place species on a scale of moral cost in research—the reader is invited to rank the following species used in HHAR: armadillos, baboons, cats, dogs, ferrets, frogs, guinea pigs, hamsters, macaque monkeys, marmoset monkeys, mice, octopi, pigs, rabbits, rats, sheep, squid, squirrel monkeys, and zebrafish. Alternatively, one could argue for various kinds of *grouping* of species in the same categories, for example, nonhuman primates in one group and all other species in another; or nonhuman primates in one group, cats and dogs in another, and all other animals in another group; or mice and rats in one group, and guinea pigs and hamsters in another group; or all these rodent species in one group; or baboons in a separate group from macaque monkeys; or baboons together with macaques and other monkey species, and so on.

If species are to be ranked, it must also be determined how much moral cost is associated with the use of each ranked species or group of species, so that it can be decided how much value an HHAR project must have to outweigh this cost. It might need to be determined whether certain ranked species or groups of species may be used in certain, but not other kinds of research. For example, it might be deemed appropriate to use monkeys in research aimed at understanding AIDS and COVID-19, but not in certain kinds of behavioral studies.

The relative moral cost view appears to be deeply engrained in the attitudes of the research community and society at large. It has, and will likely continue to have, significant effects on what kinds of animal experiments are conducted to study human disease. Therefore, if species ranking of some kind is to be retained and is scientifically and ethically defensible, the ethical core of HHAR should include one or more principles that would reflect and promote clarity and consistency regarding the ethical significance of species membership.

References

AAALAC. (2020). Association for Assessment and Accreditation of Laboratory Animal Care International. Institutional responsibilities, accreditation program FAQs, C.3. *Harm-benefit analysis*. https://www.aaalac.org/accreditation-program/faqs/#B3

AALAS. (2012). American Association for Laboratory Animal Science. *Humane care and use of laboratory animals*. https://www.aalas.org/about-aalas/position-papers/humane-care-and-use. Accessed 3 Apr 2023.
AALAS. (2021). American Association for Laboratory Animal Science. *Humane care and use of laboratory animals*. https://www.aalas.org/about-aalas/position-papers/humane-care-and-use. Accessed 30 Jun 2021
ACD. (2021). National Institutes of Health, Advisory Committee to the Director. *ACD Working Group on enhancing rigor, transparency, and translatability in animal research: final report*. https://acd.od.nih.gov/working-groups/eprar.html
ACLAM. (2017). American College of Laboratory Animal Medicine Position statement on adoption of laboratory animals. *Journal of the American Association of Laboratory Animal Science, 56*(6), 807.
ACS. (2019). American Cancer Society. *Research scholar grants policies and instructions.* https://www.cancer.org/content/dam/cancer-org/research/extramural-grants-documents/research-scholar-grants-policies-and-instructions.pdf
AES. (2020). American Epilepsy Society. *Research and training fellowship for clinicians. Policies and procedures. Use of animals in research*. https://odoo.imim.cat/web/binary/saveas?model=ir.attachment&field=datas&filename_field=name&id=773645
AHA. (1985). American Heart Association. *Position of the American Heart Association on the use of research animals*. Circulation Research 57(2):330–331.
Akhtar, A. (2015). The flaws and human harms of animal experimentation. *Cambridge Quarterly of Healthcare Ethics, 24*(4), 407–419.
AMS. (2015). *Academy of Medical Sciences, Biotechnology and Biological Sciences and reliability of biomedical research: improving research practice*. https://acmedsci.ac.uk/viewFile/56314e40aac61.pdf
AniWA. (2008). *Switzerland Animal Welfare Act of 16 December 2005 as amended. SR 455. (Eng. trans)*. https://fedlex.data.admin.ch/filestore/fedlex.data.admin.ch/eli/cc/2008/414/20170501/en/pdf-a/fedlex-data-admin-ch-eli-cc-2008-414-20170501-en-pdf-a.pdf
APA. (2012). American Psychological Association. *Guidelines for ethical conduct in the care and use of nonhuman animals in research*. https://www.apa.org/science/leadership/care/care-animal-guidelines.pdf
APS. (2014). American Physiological Society. *Guiding principles for the care and use of vertebrate animals in research and training.* https://www.physiology.org/career/policy-advocacy/policy-statements/care-and-use-of-vertebrate-animals-in-research?SSO=Y
ASIH. (2004). American Society of Ichthyologists and Herpetologists. *Guidelines for use of live amphibians and reptiles in field and laboratory research*. https://asih.org/sites/default/files/documents/resources/guidelinesherpsresearch2004.pdf
ASLAP. (2008). American Society of Laboratory Animal Practitioners. *ASLAP animal care principles.* https://www.aslap.org/media/b968fbe2-b2a8-4625-97d7-8a44506dea80/wwRmoA/ASLAP/About/animal-care-principles.pdf
ASP. (2001). American Society of Primatologists. *Principles for the ethical treatment of human primates.* https://asp.org/2021/04/20/principles-for-the-ethical-treatment-of-human-primates/
ASPA. (2016). *Animals (Scientific Procedures) Act 1986 as amended*. https://www.legislation.gov.uk/ukpga/1986/14/contents
AWA. (2015). *Animal Welfare Act. 7 U.S.C.* §§ 2131–2159.
AWAR. (2020). *Animal Welfare Act Regulations. 9 C.F.R.* §§ 1.1-3.92.
Baneux, P. J. R., Martin, M. E., Allen, M. J., & Hallman, T. M. (2014). Issues related to institutional animal care and use committees and clinical trials using privately owned animals. *ILAR Journal, 55*(1), 200–209.
Beauchamp, T. L., & DeGrazia, D. (2020). *Principles of animal research ethics*. Oxford University Press.
Botting, J. H., & Morrison, A. R. (1997). Animal research is vital to medicine. *Scientific American, 276*(2), 83–85.

Brønstad, A., Newcomer, C. E., Decelle, T., Everitt, J. I., Guillen, J., & Laber, K. (2016). 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*(1S), 1–20.

Buttke, D. E., Decker, D. J., & Wild, M. A. (2015). The role of one health in wildlife conservation: A challenge and opportunity. *Journal of Wildlife Diseases, 51*(1), 1–8.

California (2015). West's Ann. Cal. *Educ. Code* §66017.7. *Animals used for diagnostic purposes or medical research; adoption after completion of testing or research*.

Canadian Council on Animal Care. (1989). *Ethics of animal experimentation*. https://ccac.ca/Documents/Standards/Policies/Ethics_of_animal_investigation.pdf

Carbone, L. (2004). *What animals want: Expertise and advocacy in laboratory animal welfare policy*. Oxford University Press.

Carbone, L., Guanzini, L., & McDonald, C. (2003). Adoption options for laboratory animals. *Lab Animal, 32*(9), 37–41.

Carstens, E., & Moberg, G. P. (2000). Recognizing pain and distress in laboratory animals. *ILAR Journal, 41*(2), 62–71.

Cavalieri, P. (2002). *The animal question: Why human animals deserve human rights*. Oxford University Press.CCAC (1989).

Cheleuitte-Nieves, C., & Lipman, N. S. (2022). Improving replicability, reproducibility, and reliability in preclinical research: A shared responsibility. *ILAR Journal, 60*(2), 113–119.

Cigman, R. (1981). Death, misfortune, and species inequality. *Philosophy and Public Affairs, 10*(1), 47–64.

Comroe, J., & Dripps, R. (1976). Scientific basis for the support of biomedical science. *Science, 192*(4235), 105–111.

DeGrazia, D., & Sebo, J. (2015). Necessary conditions for morally responsible animal research. *Cambridge Quarterly of Healthcare Ethics, 24*(4), 420–430.

DoD. (2019). United States Department of Defense. *DoD instruction 3216.01, Use of animals in DoD conducted and supported research and training*. https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/321601p.pdf?ver=2019-03-21-074633-787

EAA. (2021). Experiments on Animals Act 1977 as amended. *Wet op de dierproeven* 12 januari 1977. https://wetten.overheid.nl/BWBR0003081/2021-07-01

EU. (2010). *Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes*. https://eur-lex.europa.eu/eli/dir/2010/63/oj

FASEB. (2017). Federation of American Societies for Experimental Biology. *Federal funding for biomedical and related life sciences research FY 2018*. https://www.faseb.org/Portals/2/PDFs/opa/2017/Federal%20Funding%20Report%20FY%202018.pdf

FASEB. (2021). Federation of American Societies for Experimental Biology. *Statement of principles for the use of Animals in research & education.* https://www.faseb.org/Science-Policy-and-Advocacy/Science-Policy-Research-Issues/Animals-in-Research-and-Education/Statement-of-Principles

Festing, M. F. W. (2020). The "completely randomised" and the "randomised block" are the only experimental designs suitable for widespread use in pre-clinical research. *Scientific Reports, 10*, 17577.

Francione, G. L. (2009). *Animals as persons: Essays on the abolition of animal exploitation*. Columbia University Press.

Frey, R. G. (1988). Moral standing, the value of lives, and speciesism. *Between the Species, 4*(3), 191–201.

Friedman, H., Ator, N., Haigwood, N., Newsome, W., Allan, J. S., Golos, T. G., Kordower, J. H., Shade, R. E., Goldberg, M. E., Bailey, M. R., & Bianchi, P. (2017). The critical role of nonhuman primates in medical research. *Pathogens and Immunity, 2*(3), 352–365.

Gallup. (2021). *Moral issues. Gallup historical trends*. https://news.gallup.com/poll/1681/moral-issues.aspx

GAWAR. (2013). German animal welfare regulation governing experimental animals of 1st august, 2013. BGBI I p. 3126. *TierSchVersV*. Eng, trans. https://www.aaalac.org/pub/?id=E905B2A2-9F98-2177-67B1-3A284785FCCA

Gay, W. I. (1984). Health benefits of animal research: The dog as research subject. *The Physiologist, 27*(3), 133–140.

Genzel, L., Adan, R., Berns, A., van den Beucken, J. J. J. P., Blokland, A., Boddeke, E. H. W. G. M., Bogers, W. M., Bontrop, R., Bulthuis, R., Bousema, T., Clevers, H., Coenen, T. C. J. J., van Dam, A. M., Deen, P. M. T., van Dijk, K. W., Eggen, B. J. L., Elgersma, Y., Erdogan, I., Englitz, B., et al. (2020). How the COVID-19 pandemic highlights the necessity of animal research. *Current Biology, 30*(18), R1014–R1018.

Greek, C. R., & Greek, J. (2000). *Sacred cows and golden geese: The human cost of experimenting on animals*. Continuum.

Grimm, D. (2021). Controversial study says U.S. labs use 111 million mice, rats. *Science, 371*(6527), 332–333.

Grimm, H., Eggel, M., Deplazes-Zemp, A., & Biller-Adorno, N. (2017). 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*, 70.

Harman, E. (2011). The moral significance of animal pain and animal death. In T. B. Beauchamp & R. G. Frey (Eds.), *The Oxford handbook of animal ethics* (pp. 796–825). Oxford University Press.

HREA. (1985). *Health Research Extension Act of 1985. 42 U.S.C. §289d*.

HSUS. (2021). Humane Society of the United States. *Alternatives to animal tests*. https://www.humanesociety.org/resources/alternatives-animal-tests

ICLAS. (2013). International Council for Laboratory Animal Science. *ICLAS ethical guidelines for researchers*. https://media-01.imu.nl/storage/iclas.org/5197/iclas-ethical-guidlines-researcher.pdf

IOM. (1991). *Institute of Medicine. Science, medicine, and animals*. National Academies Press.

Ipsos. MORI. (2018). *Public attitudes to animal research in 2018*. https://www.ipsos.com/ipsos-mori/en-uk/public-attitudes-animal-research-2018

Kaur, T., Singh, J., Tong, S., Humphrey, C., Clevenger, D., Tan, W., Szekely, B., Wang, Y., Yan, L. I., Muse, E. A., Kiyono, M., Hanamuras, S., Inoue, E., Nakamuras, M., Huffman, M. A., & Nishida, T. (2008). Descriptive epidemiology of fatal respiratory outbreaks and detection of a human-related metapneumovirus in wild chimpanzees (Pan troglodytes) at Mahale Mountains National Park, western Tanzania. *American Journal of Primatology, 70*, 755–765.

Kinter, L. B., DeHaven, R., Johnson, D. K., & DeGeorge, J. J. (2021). A brief history of use of animals in biomedical research and perspective on non-animal alternatives. *ILAR Journal, 62*, 7–16.

Kiple, K. F., & Ornelas, K. C. (2001). Experimental animals in medical research: A history. In E. F. Paul & J. Paul (Eds.), *Why animal experimentation matters: The use of animals in medical research* (pp. 23–48). Transaction Publishers.

Kol, A., Arzi, B., Athanasiou, K. A., Farmer, D. L., Nolta, J. A., Rebhun, R. B., Chen, X., Griffiths, L. G., Verstraete, F. J. M., Murphy, C. J., & Borjesson, D. L. (2015). Translational scientist's new best friends. *Science Translational Medicine, 7*(308ps21), 1–8.

Laber, K., Newcomer, C. E., Decelle, T., Everitt, J. I., Guillen, J., & Brønstad, A. (2016). 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*(1S), 21–42.

Lairmore, M. D., & Khanna, C. (2014). Naturally occurring diseases in animals: Contributions to translational medicine. *ILAR Journal, 55*(1), 1–3.

LAVA. (2016). The Laboratory Animals Association of the British Veterinary Association. *LAVA position statement on the use of animals in research*. http://www.lava.uk.net/viewtopic.php?f=3&t=26

Loew, F. M. (1988). Animals as beneficiaries of biomedical research originally intended for humans. *ILAR News, 30*(4), 13–15.

Macleod, M., & Mohan, S. (2019). Reproducibility and rigor in animal-based research. *ILAR Journal, 60*(1), 17–23.
Maurer, K. J., & Quimby, F. W. (2015). Animal models in biomedical research. In J. Fox (Ed.), *Laboratory animal medicine* (3rd ed., pp. 1497–1534). Elsevier.
Merrill, G. F. (1986). The case for the use of animals in medicine. In M. W. Fox & L. D. Mickley (Eds.), *Advances in animal welfare science 1986/87* (Vol. 3, pp. 227–243). Springer.
NASEM. (2020). National Academies of Sciences, Engineering, and Medicine 2020. *Necessity, use, and care of laboratory dogs at the U.S. Department of Veterans Affairs.*
Nevada. (2015). Nev. Rev. Stat. §574.205. *Adoption of dogs and cats at research facilities. Requirement to offer dog or cat for adoption prior to euthanization; immunity from civil liability*.
NHMRC. (2013). National Health and Medical Research Council. *Australian code for the care and use of animals for scientific purposes* (8th edn). National Health and Medical Research Council.
Niemi, S. (2020). Harm-benefit analysis can be harmful. *ILAR Journal, 60*, 341–346.
NIH. (2016a). National Institutes of Health. *Definitions of criteria and considerations for research project grant (RPG/R01/R03/R15/R21/R34) critiques*, https://grants.nih.gov/grants/peer/critiques/rpg.htm
NIH. (2016b). National Institutes of Health. *NIH research involving chimpanzees. NOT-OD-16-095*. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-095.html.
NIH. (2017). National Institutes of Health. *What we do. Mission and goals*. https://www.nih.gov/about–nih/what–we–do/mission–goals
NIH. (2018). National Institutes of Health, Grants and funding. *Peer review*. https://grants.nih.gov/grants/peer-review.htm
NRC. (2008). National Research Council. *Recognition and alleviation of distress in laboratory animals*. The National Academies Press.
NRC. (2009). National Research Council. *Recognition and alleviation of pain in laboratory animals*. The National Academies Press.
NRC. (2011a). National Research Council. *Chimpanzees in biomedical and behavioral.*
NRC. (2011b). National Research Council. *Guide for the care and use of laboratory animals* (8th edn). The National Academies Press.
NSF. (2019). National Science Foundation grant general conditions (GC-1), para. *36, Animal Welfare*. https://www.nsf.gov/bfa/dias/policy/gc1/feb19.pdf
Nuremberg Code. (1947). Permissible medical experiments. In *Trials of war criminals before the Nuremberg military tribunals under control Council Law No. 10. Nuremberg October 1946–April 1949* (Vol. 2, pp. 181–182). US Government Printing Office.
Oregon. (2019). Or. Rev. Stat. §609.410. *Disposition of dogs and cats by research facility*.
Paul, E., Sikes, R. S., Beaupre, S. J., & Wingfield, J. C. (2015). Animal welfare policy: Implementation in the context of wildlife research—Policy review and discussion of fundamental issues. *ILAR Journal, 56*(3), 312–334.
PCAL. (1994). *Israel prevention of cruelty to animals law (experiments on animals), 5754-1994 and prevention of cruelty to animals rules (experiments on animals), 5761-2001, Eng. trans.* https://www.aaalac.org/pub/?id=DCF12A06-C1B3-1978-F28F-79C2C0914FF3
Percie du Sert, N., Hurst, V., Ahluwalia, A., Alam, S., Avey, M. T., Baker, M., Browne, W. J., Clark, A., Cuthill, I. C., Dirnagl, U., Emerson, M., Garner, P., Holgate, S. T., Howells, D. W., Karp, N. A., Lazic, S. E., Lidster, K., MacCallum, C. J., Macleod, M., Pearl, E. J., Petersen, O., Rawle, F., Reynolds, P., Rooney, K., Sena, E. S., Silberberg, S. D., Steckler, T., & Wurbel, H. (2020). The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLoS Biology, 40*, 1769–1777.
Pew. (2018). Pew Research Center. *Americans divided over the use of animals in scientific research*. https://www.pewresearch.org/fact-tank/2018/08/16/americans-are-divided-over-the-use-of-animals-in-scientific-research/

Phillips, J. B., & Westerfield, M. (2014). Zebrafish models in translational research: Tipping the scales toward advancements in human health. *Disease Models and Mechanisms, 7*(7), 739–743.
Phillips, K. A., Bales, K. L., Capitanio, J. P., Conley, A., Czoty, P. W., 't Hart, B. A., Hopkins, W. D., Shiu-Lok Hu, S.-L., Miller, L. A., Nader, M. A., Peter, W., Nathanielsz, P. W., Rogers, J., Shively, C. A., & Voytk, M. L. (2014). Why primate models matter. *American Journal of Primatology, 76*(9), 801–827.
PHS. (2015). *Public Health Service Policy on humane care and use of laboratory animals*. https://grants.nih.gov/grants/olaw/references/phspolicylabanimals.pdf.Press.
Quimby, F. (1998). Contributions to veterinary medicine from animal research. *Applied Animal Behaviour Science, 59*(1–3), 183–192.
Regan, T. (1983). *The case for animal rights*. University of California Press.
Rollin, B. E. (1992). *Animal rights and human morality*. Prometheus Books.
Rollin, B. E., & Kesel, M. L. (1995). *The experimental animal in biomedical research* (Vol. II). CRC Press.
Rowan, A. (2012). Debating the value of animal research. In J. R. Garrett (Ed.), *The ethics of animal research* (pp. 197–214). MIT Press.
Russell, W. M. S., & Burch, R. L. (1959). *The principles of humane experimental technique*. Methuen & Co..
SABA. (2007). *Singapore Animals and Birds Act (Care and use of animals for scientific purposes) rules. G.N. no. S 668/2004*. https://sso.agc.gov.sg/SL/ABA1965-R10?DocDate=20190329/
SAWA. (2018). Swedish Animal Welfare Act. *SFS* 2018:1192.
SfN. (2016). Society for Neuroscience. *Policies on the use of animals and humans in neuroscience research.* https://www.sfn.org/advocacy/policy-positions/policies-on-the-use-of-animals-and-humans-in-research.
Singer, P. (1975). *Animal liberation*. Avon Books.
Smith, A. J., Clutton, R. E., Lilley, E., Hansen, K. E. A., & Brattelid, T. (2018). Prepare: Guidelines for planning animal research and testing. *Laboratory Animals, 52*(2), 135–141.
SOT. (2008). Society of Toxicology. *Guiding principles in the use of animals in toxicology*. https://www.toxicology.org/pubs/statements/Guiding_Principles.pdf
SRC. (2019) [In Swedish]. Swedish Research Council. *Allmänhetens syn på djurförsök*.
Stokes, W. S. (2000). Reducing unrelieved pain and distress in laboratory animals: Using humane endpoints. *ILAR Journal, 41*(2), 59–61.
Sztainberg, Y., & Chen, A. (2010). An environmental enrichment model for mice. *Nature Protocols, 5*(9), 1535–1539.
Tannenbaum, J. (1999). Ethics and pain research in animals. *ILAR Journal, 40*(3), 97–110.
Tannenbaum, J. (2002). The paradigm shift toward animal happiness. *Society, 39*(6), 24–36.
Tannenbaum, J. (2017a). Ethics in biomedical animal research: The key role of the investigator. In P. M. Conn (Ed.), *Animal models for the study of human disease* (2nd. ed., pp. 3–46). Elsevier.
Tannenbaum, J. (2017b). Ethics in the use of animal models of seizure and epilepsy. In A. Pitkänen, P. S. Buckmaster, A. S. Galanopoulou, & S. L. Moshé (Eds.), *Models of seizure and epilepsy* (2nd. ed., pp. 47–68). Elsevier.
Tannenbaum, J. (2019). The pursuit and advancement of knowledge as a justification for the use of animals in research. *ILAR Journal, 60*, 347–365.
Tannenbaum, J., & Bennett, B. T. (2015). Russell and Burch's 3Rs then and now: The need for clarity and definition of purpose. *Journal of the American Association of Laboratory Animal Science, 54*(2), 1–13.
Tannenbaum, J., & Rowan, A. N. (1985). Rethinking the morality of animal research. *Hastings Center Report, 15*(5), 32–43.
Taylor, K., & Alvarez, L. R. (2019). An estimate of the number of animals used for scientific purposes worldwide in 2015. *Alternatives to Laboratory Animals, 47*(5–6), 196–213.
US Principles. (1985). *US government principles for the utilization and care of vertebrate animals used in testing, research and training. 50 Fed. Reg. 1985* (p. 20864).

USDA. (2021a). *United States Department of Agriculture. Animal and Plant Health Inspection Service, 2019 Annual report animal usage by fiscal year–column D*. https://www.aphis.usda.gov/animal_welfare/annual-reports/2019/fy19-summary-report-column-D.pdf
USDA. (2021b). United States Department of Agriculture. Animal and Plant Health Inspection Service, 2019. *Annual report animal usage by fiscal year–column E*. https://www.aphis.usda.gov/animal_welfare/annual-reports/2019/fy19-summary-report-column-E.pdf
USDA. (2021c). United States Department of Agriculture. Animal and Plant Health Inspection Service, 2019. *Annual report animal usage by fiscal year–column F*. https://www.aphis.usda.gov/animal_welfare/annual-reports/2019/fy19-summary-report-column-F.pdf
USDA. (2021d). *Chickens and eggs*. https://downloads.usda.library.cornell.edu/usda-esmis/files/fb494842n/ms35v644t/r494wg73d/ckeg0621.pdf
USDA. (2021e). *Livestock slaughter 2020 summary, April 2021*. https://downloads.usda.library.cornell.edu/usda-esmis/files/r207tp32d/sj139x554/7w62g4561/lsan0421.pdf
USDA. (2021f). *Milk cows, inventory by year, US*. https://www.nass.usda.gov/Charts_and_Maps/Milk_Production_and_Milk_Cows/milkcows.php
USDA. (2021g). *Poultry slaughter 2020 summary, February 2021*. https://downloads.usda.library.cornell.edu/usda-esmis/files/pg15bd88s/f1882d39g/j6731z19s/pslaan21.pdf
Virginia. (2021). Code of Virginia, § 3.2–6593.1. *Animal testing facilities; adoption of dogs and cats*.
Walsh, N. C., Kenney, L. L., Jangalwe, S., Aryee, K. E., Greiner, D. L., Brehm, M. A., & Shultz, L. D. (2017). Humanized mouse models of clinical disease. *Annual Review of Pathology, 12*(1), 187–215.
Warfield, M. S., & Gay, W. I. (1984). Health benefits of animal research: The cat as a research subject. *The Physiologist, 27*(4), 177–189. The National Academies Press.
Webster, J. (1994). *Animal welfare: A cool eye towards Eden*. Wiley-Blackwell.

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