

Animal Care and Use in Biodefense and Emerging Infectious Disease Research:

Framing the ethical and policy issues

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Introduction

Biodefense and emerging infectious disease (BD/EID) research aimed at discovering therapies for, vaccines preventing, or diagnostics detecting human disease caused by biological agents that may be used as weapons involves the care and sometimes highly intensive use of non-human animals. The ethical use of animals in research – in particular, in research that poses harm to animals and is undertaken for the sole benefit of humans – has long been a focus of public and professional interest and concern. In this paper we examine the care and use of animals in BD/EID research, detail the ethical issues that are of particular salience to this type of research with animals, and investigate the relationship between these issues and underlying tensions in the ethics and policy of animal research more generally. We focus on three areas of ethical concern for the care and use of animals in BD/EID research: 1) the justification for animal use in BD/EID research, especially in BD-only research and in research aimed at developing medical counter measures (MCMs) for US government stockpiling, 2) the use of nonhuman primates, and 3) the care and use of animals within animal biosafety level (ABSL) 3 and 4 laboratories. Since there is no adequate overview of the ethical issues specific to BD/EID care and use of animals available to researchers or others interested parties, we hope this paper can serve as a starting place for informed discussion of these issues.

We highlight in this introduction three background points that we believe are generally significant with respect to the ethical issues involved in BD/EID research on non-human animals. First, the salient ethical issues for BD/EID research are no different

in broad theoretical kind from those for other types of animal research involving harm to animals for the sake of human benefit. These include the moral justification for research on animals for the sake of human benefit, the relative moral status of human and non-human animals, and issues of relationship and character. The specific contours of these ethical issues in the context of BD/EID research, however, are highly morally significant. For example, some features of BD/EID animal research (including orientation towards biodefense aims, the sometimes intensive use of non-human primates, and high containment laboratory settings) create especially salient examples of these complex moral issues.

Second, we note that there is a conceptually loose, but practically quite significant, distinction that may be drawn between the approach to ethical issues in BD/EID research internal to those research practices (e.g. the “ethics” of institutional and government regulations, guidance and policy and the responsible conduct of science) and an external approach to the ethical issues involved in this research. The “internal” ethics approach facilitates BD/EID research by promoting concordance with institutional, government, and science community ethics norms and guidance. This approach assumes the moral permissibility of many of the animal uses involved in BD/EID research and seeks to promote animal welfare and limit animal harm within this research. The “external” approach addresses broader moral issues and theoretical frameworks such as those mentioned above and, in particular, is concerned at the outset with whether certain human uses of animals are morally justifiable. Importantly, we think that both of these perspectives (e.g. ethics “internal” and “external” to BD/EID research practices) could be enriched by careful attention to the other. In this paper we attempt to characterize, and to

relate to one another, the ethical issues involved in BD/EID research guidelines, regulations, and practices and broader philosophical ethical frameworks and issues.

Our third general point is more a note about method. We found that different philosophical moral frameworks were more or less relevant to the different specific ethical issues we have identified in BD/EID research. Thus we have taken a kind of philosophical pluralist approach in addressing different specific philosophical frameworks and core issues for each area of ethical concern in BD/EID research. In particular, in addressing the justification for BD/EID research uses of animals we consider the relationship between an apparent appeal to consequentialist moral reasoning and issues of animal moral status. In addressing the use of non-human primates in this research we focus especially on human and non-human relative moral status concerns. For issues related to BD/EID research environment and animal care and use practices, we engage the topics of care and relationship through a virtue ethical framework.

The paper is divided into three parts. Part 1 offers an overview of BD/EID research in the US and of the general regulatory and ethics frameworks relevant for the care and use of animals in biomedical research generally, since these are also relevant for BD/EID research. Part 2 addresses the three areas of interest for the care and use of animals in BD/EID research mentioned above ((1) the justification for animal use in BD/EID research, especially in BD-only research and in research aimed at developing medical counter measures (MCMs) for US government stockpiling, (2) the use of nonhuman primates, and (3) the care of animals within animal biosafety level (ABSL) 3 and 4 laboratories) and discusses in detail how these relate to broader philosophical ethical issues about the care and use of animals in biomedical research introduced in part

1. Part 3 offers some discussion of possible policy applications and suggestions for areas of further work.

Part 1: Current BD/EID research context and general ethical and regulatory context

Section A) BD/EID research context

There is a long history of BD research in the US and elsewhere, but its combination with EID research, the ramping up of federal funding for research involving “priority pathogens”, and the focus on MCM production (vaccines, diagnostics, and therapeutics) help to shape the current research context.¹

At first it might appear that BD and EID research are quite strange bedfellows. BD research focuses on biological, chemical, nuclear, or radiological agents that could be used as weapons by states, criminals, or terrorists. Current examples of BD research might be development of MCMs to “weaponized” smallpox (no longer a naturally occurring disease) or anthrax. EID research, on the other hand, commonly focuses on emerging and re-emerging infectious diseases with significant public health impact, such as HIV/AIDS, SARS, Ebola virus, or drug-resistant tuberculosis. However, historically these two kinds of research have crossed paths in military context as MCMs for EIDs have been employed in the US since the Revolutionary War to protect troops from naturally occurring epidemic diseases like smallpox and malaria (Anderson & Swearingen, 2006). Further, the use of naturally occurring infectious diseases of both

¹ LouAnn Burnett provided this summary of what is different about BD/EID research in the current context in personal communication.

animals and humans as bioweapons in military settings has a centuries-long history, including agents as diverse as smallpox, anthrax, and tularemia.

The contemporary focus of combined BD/EID research is on those EIDs that may be “weaponized,” as well as on agents (such as smallpox) that are not currently emerging infectious diseases but pose a biothreat. These so called “priority pathogens” are listed by the US National Institute of Allergy and Infectious Disease (NIH NIAID, 2008 Mar 10).

The overarching aim of BD/EID research in the current US context has been the development of MCMs for use against these priority pathogens. To this end, increased funding for research, facilities, and purchase (“stockpiling”) of developed vaccines, diagnostic tools, and therapeutics has been granted by the US government since 2001. To give just a few examples: Project BioShield, signed into law in 2004, set aside \$5.6 billion for purchase and stockpiling of MCMs and other BD efforts (US Department of Health and Human Services, n.d.). NIAID oversees grants for 10 regional centers of excellence (RCEs) for emerging infections and biodefense, to support research focused on countering threats from bioterror agents and emerging infectious diseases (NIH NIAID, 2008 Sep 12) (NIH NIAID RCE Resource, n.d.). Finally, according to a US Government Accounting Office (GAO) report on “High-containment Biosafety Laboratories,” the number of the highest bio-safety level (BSL 4) labs increased in the US from a total of 5 before 2001 to a total of 15 either planned, built, or “in the works” by 2007 (US GAO, 2007). These labs contain the most dangerous pathogens and must meet very strict safety and security regulations as well, of course, as facility structure requirements.

Like animal use in biomedical research generally, animal use in BD/EID research fits into “basic” and “applied” research categories, where basic research focuses on appropriate animal “models” for study of the pathogens and on the course and transmission of the diseases, and applied research focuses on the development of medical products for human benefit or amelioration of harm.² However, animal use in BD/EID research also has distinct features: it takes place in high containment (animal bio-safety level (ABSL) 3 or 4) laboratories, focuses on the development of MCMs for human disease without necessarily including efficacy studies in human subjects, and may be motivated, in some cases, primarily by BD aims rather than as a response to naturally occurring disease patterns. We will discuss how each of these specific aspects of the BD/EID research context raises ethical issues for animal care and use below, but first we provide an overview of the regulatory and ethical frameworks that are relevant for biomedical research care and use of animals generally, since these frameworks also apply to BD/EID research.

Section B) US animal care and use regulatory and ethics frameworks

The care and use of animals in biomedical research studies is highly regulated in the United States. The ethical issues involved in modern biomedical research uses of animals has been the subject of a revival of attention, both in popular news media and in philosophical and other academic literature, at least since the 1960’s. The general regulatory framework for animal care and use is common across all types of biomedical research. The fundamental ethical issues raised by animal research –the moral

² According to a recent RCE program evaluation, 51% of funded projects generally within the RCEs are basic research, including basic sciences, genomics, immunology, pathogenesis, proteomics and structural biology (Concept Systems Inc., 2008, p. 21).

justification for research on animals for the sake of human benefit, issues of the relative moral status of human and nonhuman animals, and issues of relationships and character – likewise do not change with the type of research.

i) *Animal care and use regulations and guidance*

In the United States, the care and use of animals in biomedical research is regulated by: 1) the Animal Welfare Act (AWA of 1966 as Amended, 1996), administered by the Animal and Plant Health Inspection Service (APHIS) within the United States Department of Agriculture (USDA) and 2) the U. S. Public Health Services Policy on Humane Care and Use of Laboratory Animals (in compliance with the Health Research Extension Act of 1985), implemented by the Office of Laboratory Animal Welfare (OLAW) under the National Institutes of Health (NIH). Also significant is the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), a private non-profit organization providing voluntary accreditation and assessment (AAALAC International, n.d.).

The Animal Welfare Act primarily addresses the transportation, procurement, and sale of animals, and regulates laboratory and other animal use. It underwent significant changes in 1985 when requirements were added to address: oversight by institutional animal care and use committees (IACUCs), primate psychological well-being, exercise for dogs, and other clarifications regarding laboratory animal welfare requirements (US Animal Wellness Information Center, n.d.; US OLAW, 2007 Mar 27). Regulations interpreting and applying the AWA are found in Title 9 of the Code of Federal Regulations, Chapter 1, (USDA, 2009, 9CFR Parts 1 and 2). These regulations do not

apply to birds, mice of the genus *mus*, and rats of the genus *rattus* bred for research, although mice and rats account for the largest percentage of animals used in biomedical research. The AWA also does not cover “cold blooded” vertebrate animals, or farm animals used in agricultural research (USDA, 2009, 9 CFR1.1). Compliance with the AWA is ensured by twice yearly inspections by IACUCs (USDA, 2009, 9 CFR2.31(c)).

The PHS Policy for Humane Care and use of Laboratory Animals applies to research funded or conducted by PHS agencies using vertebrates. The PHS Policy requires that labs follow the animal care and use guidance developed in the *Guide for Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1996) and is implemented and interpreted by the NIH Office of Laboratory Animal Welfare (OLAW) (NIH OLAW, 2000 Mar 27). The PHS policy includes the “United States Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training” (NIH OLAW, 2002 Aug 1) (hereafter “Principles”). The office requires written assurances of compliance with policy principles and the *Guide* and inspects only for cause, but has the power to withhold federal funds. Both the PHS Policy and the AWA require research oversight by IACUCs.

AAALAC laboratory accreditation is considered important for attracting funding and researchers, and can also cover industry research that does not fall under the PHS policy. This accreditation requires inspections every 3 years with notice (AAALAC International, n.d.).

This framework, which provides a highly regulated context for animal care and use, is also not without oddities. For example, some animal research could fall outside of any of these oversight mechanisms (research in a non-AAALAC accredited laboratory

using mice, birds, rats or “cold blooded” animals that is not funded by a PHS agency, or research on non-vertebrates even if it is funded by a PHS agency), while other research is covered by all three (federally funded research on warm blooded animals other than mice, rats, or birds taking place in AALAC accredited facilities). Fortunately for those researchers for whom all three sets of guidelines are relevant, since 1991 the USDA and OLAW have approached the regulations in a way that “harmonizes” them as much as possible and focuses on outcomes relating to animal welfare (performance standards) rather than on more rigid specific requirements for care (engineering standards), in accordance with an official Memorandum of Understanding between the FDA, USDA, and NIH (Sideris, McCarthy, & Smith, 1999, p. 13). This focus on performance standards rather than on specific requirements of care, while offering increased flexibility, can at the same time pose potential problems for protecting animal interests. (Walker, 2006; DeHaven, 2002).

ii) *Regulations, policies, and ethics*

While those concerned to protect and further animal interests generally view a more regulated research environment as better, morally speaking, it is also true that “Regulation can act as an emotional screen between the researcher and an animal, possibly encouraging researchers to believe that simply to conform to regulations is to act in a moral way” (Nuffield Council on Bioethics, 2005, p. 21). It is important, therefore, to emphasize the difference between regulatory compliance and ethics from the point of view of researchers as moral agents. While regulations may be perceived as rules enforced by government and/or institutions, moral or ethical norms guide agents through

the assumption of individual responsibility and character development. Once a particular regulatory and institutional framework is in place, the persons having the most direct impact on the well-being of animals used in research are researchers, laboratory technicians, staff and others “in the lab.” Thus, regulations regarding animal care and use may be most effective in protecting and furthering animal interests when they support and enhance the opportunities of these individuals for moral education, their habituation in the proper virtues of care, and their assumption of responsibility for promoting animal welfare and limiting animal harms. We shall further address these issues below, in part 2.C(on animal care and use in ABSL 3 and 3 laboratories) and, in broader terms, in part 1 D.ii.

It is also necessary to keep in mind an important justificatory distinction between regulatory and policy guidance on the one hand, and ethical guidance on the other. Unlike ethical guidance, regulations and policies may depend on purely organizational, pragmatic, or political justification. It is always appropriate to ask whether the requirements of a regulation or policy are morally good, bad, or a matter of indifference.

Notwithstanding these important distinctions between ethical and regulatory guidance, we can address which aspects of the US regulatory structure are most closely associated with ethical guidance (and, indeed, sometimes pass for “ethics” proper within the research setting). First there are the IACUCs. These committees offer the most hands-on oversight of animal research within the regulatory structure and have the most input, from a regulatory standpoint into the actual care and use of animals in particular protocols. IACUCs make sure, among other matters, that the numbers of animals used are appropriate to the scientific aims of the study, that animals are not subjected to pain or

suffering that is not justified by the scientific aims of the research, and that the facilities are maintained in a way that conforms to US animal care guidance. While IACUCs attend to issues like these that directly affect animal welfare or well-being, they do not generally consider broader ethical issues, such as whether the research is itself justified on a weighing of overall costs to the animals vs. potential benefits of the research. In fact, they are generally precluded by regulation from such considerations (USDA, 2009, 9 CFR 2.31(a)). This limitation stands in particular contrast to the ethical review of animal research that takes place in many European Union countries, as we discuss in part 2.A.iv (on the relationship of a consequence based justification for certain animal uses to the moral considerability of animals).

Next are the PHS Policy “Principles” (US Office of Lab and Animal Welfare, 2002 Aug 1). The preamble to these principles states the overall justification of animal testing as “The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals,” and many of the subsequent stated guiding principles have ethical content or implications. For example, principle II calls for “due consideration” of the potential for benefit from particular uses of animals, principle III asks for “consideration” of alternatives to animal use and requires reduction in the numbers of animals used to the minimum needed for the scientific aims, and principles IV-VI specify that animals should be assumed to experience pain where human pain would be probable, aim to minimize pain experienced by animals, and call for painlessly killing animals when pain cannot be minimized. However, these principles are not viewed as absolute requirements; exceptions can often be made with appropriate review.³

³ For a discussion of the implications of this point for the ethical framework for animal use in biomedical research see Walker (2006).

As an overarching framework guiding animal research ethics, the so-called “3Rs” of animal research are widely accepted by the international biomedical research community and reflected in the PHS Policy Principles (above) and in IACUC oversight practices within the US⁴ This framework calls for the reduction, refinement, and replacement of animals used in biomedical research. We discuss the 3R model and its interpretation within the PHS “Principles” in more detail in part 2.A.v.

Section C) The ethics of animal care and use in research: a persisting tension

Since the origins of modern forms of this research in the 19th century, research using animals has been generally viewed as vital to human health; likewise, since its earliest uses, animal research has been denounced by some (for example, the antivivisection movement, which also began in the 19th century) as animal cruelty. In the US, to the extent that there is current popular attention to the ethical issues involved in animal research, this seems to have its roots in part in the social movements of the 1960s, such as environmentalism and civil rights, which were then linked to animal interests (Sideris et al., 1999). This linkage arose in part from the changing nature of both farming and biomedical research (Rollin, 2005, p. 112), and in part because of news media coverage of troubling animal research practices. Both the initial passing of the Animal Welfare Act in 1966 and the passage in 1985 of the Health Research Extension Act were facilitated by public attention to perceived ethical misconduct within research. The Animal Welfare Act was, in part, a response to a 1966 story in LIFE magazine about

⁴ For international support, see for example the CIOMS 1985 statement (CIOMS, 1985), the European Partnership for Alternative Approaches to Animal Testing (EPAA, n.d.), and the 3R Research Foundation of Switzerland (n.d.).

the use of dogs in research, titled “Concentration Camp for Dogs.”⁵ The 1985 act resulted in part from public concern about head injury studies conducted in baboons at the University of Pennsylvania and in the Silver Springs Monkey case (Sideris et al., 1999, p. 11). Despite these sometimes notorious examples, animal research is generally supported by the US public, although views about particular research vary depending on the perceived value of the research, its potential for animal suffering, and the type of animal used (Pious, 1998).

We turn now to an overview of philosophical ethics and animal research. That examination is followed by more detailed discussion of the ethical issues specific to the care and use of animals in BD/EID research.

Section D) Philosophical Ethics and Animal Care and Use

In this section, we introduce philosophical frameworks that are relevant to the ethical issues in potentially harmful animal research undertaken primarily for human benefit. At a practical level, we see three primary roles for this philosophical framing: 1) To provide a normative framework for considering, assessing, and enriching the roles of researchers (and others) in relationship to animal research subjects; 2) To provide a way to conceptualize, protect, and further animal interests within research; and 3) To address issues of justification for animal uses in research, both generally in uses that are harmful to animals and done for human benefit, and in specific contexts relevant to BD/EID research.

⁵ The story was on 4 Feb 1966, pp. 2-29. The interpretation of the link to the AWA is from Rollin (2005, p. 113) and Bishop & Nolen (2001, p. 3).

In very general terms, we might think of 1 and 2 above as attending to the ethical issues that are in the foreground for animal researchers and care-takers involved in research. It is through these practical engagements, then, that philosophical ethical framing is most likely to address concerns at the forefront of ethics “internal” to animal research. It is noteworthy, however, that issues of justification for animal use, 3 above, have instead dominated the philosophical literature on animal research. In other words, the philosophical literature has focused on the ethical issues “external” to research by asking whether, or to what extent, harmful animal research for the sake of human benefit is justified. One of our goals in this paper is to acknowledge and develop the relationship between consideration of the ethical issues internal to the practice of animal research and the issues regarded as external to that practice. Although distinguishable in important ways, these considerations are also meaningfully intertwined.. We think it important for animal researchers to address the broader questions of moral justification and to consider certain moral limitations on permissible animal uses. In addition, relevant philosophical frameworks and theoretical perspectives help to promote animal and human flourishing and responsible care-taking internal to the practice of animal research. Thus, we consider specifically how the question of justification for animal research of various types relates to philosophical issues of animal moral status and how a virtue ethics framework might better address issues internal to research practices.

i) Moral Status

If a being or thing has moral status or standing, we are “obliged to give weight in our deliberations [and actions] to its needs, interests, or well-being.” (Warren, 2000, p. 1).⁶ This status might be direct (attributable to the being or thing itself) or indirect (attributable to the being or thing in virtue of its instrumental value, for example). It may also be full (that is, in effect, equal to the status of a person) or partial (any lesser status). Importantly, questions about the moral justifiability of research often require treatment of the question of relative animal moral status. For example, the Nuffield Council’s report “The ethics of research involving animals” identifies as critical the issue of how to justify the “use of animals in research where the use of non-consenting human participants would be unacceptable” (Nuffield Council, 2005, p. 38). Three possibilities are presented: 1) Argue that the animals involved have less moral standing than human beings; 2) Argue that the animals’ interests are different from human interests such that it matters less to the animals to be used in these ways; or 3) Argue that the research is so important that it must be done even though it is, in another sense, wrong to do (Nuffield Council, 2005, p. 38). In section 2.Bii, (on non-human primate moral status and BD/EID research), we discuss in much more detail the first and second options mentioned for justifying such research. Here we simply wish to note the important tie between questions of research justification and issues of moral status.

In considering issues of moral status, we think it is helpful to distinguish two questions. The first question is: “What sorts of things are directly morally considerable?” The second question is, “Of those things that are directly morally considerable, what is

⁶ For a helpful overview of philosophical approaches to issues of animal moral status see also Gruen (2003).

their relative moral status?”⁷ We address each question briefly in turn here, and in more detail in later parts of the paper. When asking the first question, what we want to know is which sorts of things (beings or objects) are ones the welfare, interests, or integrity of which must be taken into account for the sake of that object or being itself (the interests or welfare of other beings aside). We are not yet necessarily asking questions about the relative weight of that consideration and so, specifically, not yet asking questions about competing claims on resources or other contexts in which we must choose between the interests, needs, or welfare of various beings (or integrity of things). The alternatives to direct moral consideration are indirect moral consideration on the one hand, for example when we consider the well-being of an ecosystem not for its own sake but because it is important for our well-being, and non-moral consideration on the other, for example when we think that it is important to maintain a species of animal for its contribution to our aesthetic appreciation.

With respect to the issue of direct moral consideration, philosophical views vary quite widely, as some think that even works of art and natural artifacts are directly morally considerable (see, e.g., Hacker-Wright, 2007), and others appear to hold that only rational beings are directly morally considerable (this is at least a plausible reading of 18th century philosopher Immanuel Kant’s view). On this issue, we think there is plausible common ground available between animal protection groups and researchers that at least all animals capable of feeling pain are directly morally considerable.

However, as we explore in more detail in section 2.A.v below (on the justification of

⁷ This distinction follows that made by Kenneth E. Goodpaster (1978), though too often ignored in subsequent literature on moral status.

BD/EID animal use for human benefit), we think the regulations in the United States are somewhat internally contradictory on this point.

Let us at least suppose that many non-human animals are morally considerable. The second question (as indicated above) is about the relative moral significance of that standing. Answering this question may be important for practical moral decision making when, for example, satisfying the needs or interests of one group of beings involves not satisfying the needs or interests of some other group of beings (as in some distributive justice questions) or, as in the case of some animal research, when benefiting one group (human beings) may involve harm to another without benefit (non-human animals). While these types of situations raise many moral questions that are best addressed in specific contexts, basic issues of relative moral standing (that is, the relative moral significance of the needs, welfare, or interests of the parties at issue) are sometimes hard to avoid.

In the case of human beings we commonly hold as a core tenet of our modern morality that “all humans are equal”—where what we mean by this is equal in terms of moral status. However, debates about the distribution of scarce resources to patients in persistent vegetative states, conflicts over the morality of abortion, and objections to the use of embryonic stem cells in research are, at least in part, grounded in views about the relative moral status of the beings at issue. In part to deal with such conflicts, a distinction is frequently made in philosophy between persons and other beings, where persons are the paradigm examples of beings with full moral status and “personhood” is morally, not biologically, determined.⁸ The philosophical notion of “person” is of a being

⁸ See, for example, Warren (1973) and Tooley (1998). The distinction, however, has a much deeper philosophical history and is invoked, for example, by Kant but not as a means of solving issues of practical

with a certain set of morally relevant intrinsic properties or capacities.⁹ In contrast to the assumption that all humans are morally equal, then, the “personhood” view of moral status is that all persons are equal, where we leave open the possibility that some humans are not persons and that some animals (or even extra-terrestrial beings) might be persons.

In contrast to the modern view that all human beings have equal moral status, it is fairly common to view non-human animals as having somewhat lesser relative moral status. However, when one sees moral status as an issue about intrinsic properties or capacities of individual beings, it becomes harder to maintain this view. Thus the so-called “argument from marginal cases” has been a key feature of philosophical views questioning the “common sense” view about the relative moral status of human vs. non-human animals. One way of spelling out the steps in this argument is as follows:

- a. Humans usually have “high level” intrinsic, seemingly morally relevant properties, such as capacity for autonomous action and choice.
- b. But these properties don’t ground certain basic rights (not to be killed for food, subjected to painful experiments etc.), because even humans without these “high level” intrinsic properties have these basic rights.
- c. These basic rights are grounded in other morally relevant intrinsic properties (such as sentience or “subjecthood”).
- d. Many non-human animals also have these properties.
- e. Equal consideration of like interests (or “moral consistency”) requires extending these same rights (or equal consideration of like interests) to all creatures with the same intrinsic properties (sentience or subjecthood).¹⁰

In this argument, the differences and similarities between the two major “camps” of philosophical views promoting a reconsideration of animal moral standing become

application such as those discussed. Indeed, his particular view creates more problems for practical application than solutions, since he holds that only rational beings with wills have full direct moral status—and that this is the only sort of moral status there is.

⁹ What these properties are varies too widely to canvas in this brief introduction. Tooley (1998) offers a list of seventeen properties that have been appealed to by philosophers (p. 120).

¹⁰ This particular way of spelling out the argument is inspired by Elizabeth Anderson’s treatment (2004, pp. 279-280)

apparent. One way of addressing the argument is through the equal consideration of like interests. This is a core part of the utilitarian approach to animal moral standing, as promoted in its best-known form by philosopher Peter Singer (1993, 1995). The other way of addressing the argument is through the promotion of equal rights for all beings sharing a certain core set of capacities (such as is contained in the notion of “subjecthood,” rather than “personhood”). This is the view promoted most prominently by Tom Regan (2004). In this paper, we don’t make much of the differences between the rights-based approach to animals and the utilitarian approach. While these approaches are very different in terms of background normative moral theory presumptions, they share many practical moral goals with respect to the changes they support for our treatment of animals.¹¹

As highlighted by the Nuffield report’s framing, we think that questions of animal moral standing (or status) are generally important in considering the justification for experimental uses of animals that would be considered morally impermissible for non-consenting human subjects, but they are particularly salient in considerations of non-human primate use in the context of some types of BD/EID research. We will discuss these issues in detail in part 2.B.ii below (on primate moral status).

¹¹ Indeed, Regan and Singer have co-edited works promoting equal consideration of animals’ interests and/or rights, and Singer has been a prominent figure in the movement promoting rights for great apes. In terms of specific practical differences between the views with regard to animal research, the rights-based view is more abolitionist than the utilitarian view. On Regan’s view, any animals that are ‘subjects of a life’ (where this has a certain technical meaning) have a right not to be used in harmful experiments for the sake of human benefit (Regan, 2004, p. 387). In contrast, on Singer’s view, the moral permissibility of animal experimentation depends on overall calculations of utility (Singer, 1993, p. 67). The crucial aspect of the view, however, is that animal interests that are similar in nature to human interests receive equal consideration in that calculation.

ii) *Virtue ethics and agent character perspective*

Virtue ethics offers an approach to normative moral theory that is quite different from either a utilitarian or a rights-based view. However, unlike utilitarianism or rights views of ethics, virtue ethics has not been widely used in consideration of our moral obligations toward non-human animals.¹² We consider this a deficit to be rectified, since this approach to ethics holds great promise, in particular with regard to the ethical issues internal to the practice of animal research. We detail much of this specific application in section 2.Civ below (on virtue ethics and high containment laboratories); here we introduce virtue ethics as a framework that seems particularly appropriate for laboratory research science in general.

Virtue ethics has its theoretical roots in ancient Greek and Chinese approaches to the question of how to live well as a human being—that is, how to live a good life.¹³ A “good life” in this sense means one that expresses human excellences of character; it does not refer to modern connotations of the “good”—i.e., comfortable or enjoyable—life. In both ancient and modern forms of virtue ethics, human character traits—or virtues and vices—are at the same time the units of moral analysis and the specific forms of human excellence. That is, if we want to know whether a given response to a dangerous situation is morally good or bad, we should ask whether it is courageous (or expressive of other relevant virtues) or rash or overly fearful (or expressive of other relevant vices). When we answer that question, we are, at the same time, answering the question whether the response is an excellent human response and, as a sort of yardstick, we look to a comparison with ideal examples (“what would [virtuous person X] do?”).

¹² Rebecca Walker (2007) offers a discussion of a virtue ethics approach to our obligations toward animals.

¹³ In this paper we mostly appeal to Aristotelian and neo-Aristotelian forms of virtue ethics.

Virtues and vices, for their part, are the already mostly familiar traits of character -- such as kindness, compassion, truthfulness, and loyalty to promises on the side of virtue and, on the side of vice, meanness, cruelty, dishonesty and infidelity.¹⁴ These traits of character are, generally, forms of human excellences (or excesses or deficiencies) relative to specific types of universal (or nearly universal) human spheres of activity that involve general types of problems and needs -- such as trust, sharing of resources, collaboration in projects, child rearing and caring, personal commitments, etc.¹⁵ Of critical importance, virtues are not simply attitudes, emotional responses, or reactions. They are “multi-track” dispositions (Hursthouse, 2007a) regarding actions, perceptions, and emotions of the right sort, toward the right subjects, for the right end, at the right times, and in the right way (Aristotle, 1985, 1106b20). As dispositions, moral virtues are reliable practical habits of character; they are neither one-time-only actions nor merely intellectual conclusions (although there are virtues of the intellect as well as of morality).

From this general overview of virtue ethics, it might not be immediately obvious why this framework is such a potentially good fit for ethical issues internal to laboratory research science practices. In spelling out the nature of this fit, it is important to be specific that what is wanted here is not necessarily a broad ethic of human excellence, but an ethic of excellence in the specific practices and habits relevant to animal research care-

¹⁴ These are just a very few examples. The virtue ethics literature is highly varied regarding which specific character traits count as virtues/vices. Aristotle offers a select list, while some modern virtue projects list literally hundreds. Further, some virtues and vices are nameless or only awkwardly named.

¹⁵ For a detailed treatment of the claim that non-relative virtues based on universal forms of human life are possible, see Nussbaum (1993).

taking and use (or, as discussed here, laboratory research more broadly).¹⁶ In medical ethics in particular, a virtue-based approach to professional ethics has received some significant support, though it is still given relatively less attention than the more predominant principle-based approach.¹⁷ While, as we shall argue next, a virtue ethics approach is also highly appropriate to a research science setting, acceptance of this framework can be seen more in the embrace of such core virtues as scientific integrity than in a specific theoretical stance.¹⁸

We turn now to a discussion of two points supporting the use of a virtue ethical approach to laboratory research ethics issues: the familiar and comprehensive nature of the virtues and the focus on contextual ethical decision-making and habituation in good practices. A third point about the good fit between animal research ethics and virtue ethics concerns the organizing concept of flourishing as an alternative to animal “welfare,” and is specific to laboratory animal research. We hold off on a discussion of this point until part 2.C.iii, where we consider the relationship of flourishing to welfare issues for animals in high containment laboratories. The two points addressed here are more general points in favor of virtue ethics as an approach to professional ethics for research scientists.

One significant reason that virtue ethics as a frame for moral issues in science research generally, and animal research in particular, has not received more explicit

¹⁶ This is important in so far as the possibility of a virtue ethics approach to this particular area of human activity does not depend necessarily on answers to more general questions about the nature of human excellence or flourishing as such. (see, e.g., Pellegrino, 2007; Dubois, 2004).

¹⁷ For a discussion of the ACGME General Competencies as signaling a turn to a virtue ethical approach to medical ethics education, see Doukas (2003). For a virtue-based discussion of clinical medical ethics, see Dwyer (1994). A variety of professional role virtue ethics accounts within medicine is offered in Walker & Ivanhoe, Eds. (2007). See in particular the chapters by Pellegrino; Baier; Radden; Blustein.

¹⁸ Dubois (2004, p. 387) discusses the use of virtue language in the National Academy of Sciences’s *On Being a Scientist: Responsible Conduct of Research*.

discussion is that this way of approaching ethical questions may go by unrecognized as *ethics* at all. The language of character (virtues and vices) is understood without explicit theoretical background, and is readily employed in moral descriptions of action (as cruel or compassionate, generous or stingy and so forth). This relative lack of a need for academic ethics as such (though not a lack of a need for practical ethics education!) is also a key reason why this framing of ethical issues fits so well in the practice of good science. Virtue ethics in this context is not learning new or specific rules for “ethical” action then applied to familiar contexts, but approaching ethical issues and questions with already familiar moral concepts and terms. These familiar concepts and terms, moreover, tie in comprehensively with morally significant features of action, feeling, and perspective. As already discussed, virtues “multi-track” these various components of appropriate ethical responses, thus making clear that ethics is neither a side-issue in the practice of science nor simply a matter of regulatory compliance.¹⁹

The second aspect of “good fit” between virtue ethics and science research professional ethics is the focus on moral decision-making as necessarily contextual and the concomitant significance of character and appropriate practice and mentorship. When properly cultivated, an agent’s own emotions, attitudes, and reasoning determine the morally appropriate response to a given context. These same functions also serve as “warning bells” in morally problematic situations. Because good character internalizes appropriate moral responsiveness, a virtue ethics approach to professional ethics in science does not belittle the moral integrity of scientists by treating them as in need of

¹⁹ Recall the important point made in the Nuffield report about the need to avoid seeing ethics as a matter of regulatory compliance. Note, however, the interesting suggestion of Dubois (2004) that regulatory compliance, given very different modes of development and education, could itself become a kind of scientific virtue.

moral education in the form of rules for action; nor does it rely merely on “spot shooting” isolated moral problems in research through ethics oversight.²⁰

Why is this the case? In virtue ethics, the organizing moral virtue is practical wisdom, or the ability to perceive accurately both the morally salient features of a particular context and the appropriateness of specific responses. Excellence in practical reason is very different from a deductive exercise in the application of particular principles to a given context. Instead it involves finely honed sensitivities for “seeing as”—that is, for recognizing moral salience—and for appropriate responsiveness that, while not “gut” reaction, is nonetheless an immediate response of applicable virtues of character. The somewhat intuitive nature of the response is, importantly, the result of continued and extensive practice—or habituation—rather than “mere feeling”. Thus, in virtue ethics generally, the importance of practical moral education cannot be overstated, and in professional virtue ethics for scientists, the importance of appropriate and sustained mentorship in the ethical practice of science is crucial.

We end this part of the paper with two caveats about the distinction we have been making between ethics internal and external to the practice of animal research, and about the potential fitness of virtue ethics to address internal ethical issues and the relevance of moral status claims to external ethical issues -- such as the moral justification of animal research in general, and BD/EID research in particular.

First, as we have already suggested, the issues of justification of animal use, promoting animal interests and welfare, and research science professional ethics (in particular, issues of character and relationship) overlap in many ways. Each of the ethics

²⁰ We are in no way suggesting that ethics oversight is inappropriate, merely that it is radically insufficient as a way of ensuring the moral practice of science.

frames we have discussed fits these various considerations to at least some extent. Regarding overlap of the issues, we have already noted that research scientists should and do think about the moral justification of their research. Furthermore, the particular care and condition of animals in research (i.e., animal welfare considerations) are highly relevant in determining whether any specific research is justifiable. Virtue ethics, which we have discussed as a philosophical frame especially salient to the ethics internal to animal research, also provides important relevant considerations regarding justification (which we discuss, albeit briefly, in part 2.C.iv). Finally, the moral status issues we discuss in terms of justification also have the potential to provide guidance regarding ethical issues internal to animal research, in so far as they map onto broader normative moral theories. Thus, the distinctions we have articulated between ethics internal to and external from the practice of animal research are (perhaps not surprisingly) somewhat less neat than they may have initially seemed. Still, as touchstones for practical analysis, we believe they have considerable value.

The second caveat is that in any larger treatment of the philosophical issues in animal research, we would need to discuss in more detail how the various frames discussed here relate to one another and how we ought to treat the conflicts that arise between these views. For example, we would need to deal with the complex issue of how virtue ethics relates to questions of moral status and the rich ways in which various forms of utilitarianism and rights-based ethical theories incorporate concerns for virtue. It is sufficient for our purposes to note, first, that because virtue ethics takes into account the proper objects of virtue, the issue of moral status is relevant. Modern virtue ethicists disagree, however, over the manner in which virtue ethics should approach moral

status.²¹ Second, any full normative moral theory, whether deontological (that is, duty-based, such as with a rights view), or consequence-based (such as utilitarianism), addresses the virtues that ought to be cultivated in order to meet the normative demands of moral life as understood within the theory. Our discussion of virtue ethics as a distinctive approach to moral theory²² does not deny the relevance of specific virtue theories to either utilitarian or rights-based approaches to morality. Instead, we present virtue ethics as a moral frame that is both undervalued and particularly helpful to the ethics of animal research.

Part 2: Ethical issues for BD/EID research on animals

We now turn to a discussion of the ethical issues raised by particular aspects of BD/EID research aims, practices, and environment. We address in turn: 1) justification for animal use, 2) the use of nonhuman primates, and 3) the care of animals in ABSL 3 and 4 laboratories. In addressing these issues we examine the key features of BD/EID research that raise the apparent ethical issues; engage the ethics framework internal to biomedical research for each area of concern; and offer philosophical framing and discussion of the core ethical tensions. In terms of philosophical framing, the first and second set of issues (justification of BD/EID research and the use of nonhuman primates) will address, in particular, issues of moral status broadly considered, while the issue of care of animals in ABSL 3 and 4 laboratories will be considered with respect to a virtue ethical framework.

²¹ Hursthouse (2007b), for example, prefers that discussions of ‘inherent worth,’ which bring with them issues of relative moral status, be understood only colloquially within virtue ethics.

²² The distinction between virtue theory and virtue ethics is laid out nicely by Julia Driver (1998).

Section A) Animal use justification in BD/EID research

BD/EID research is one of many areas of biomedical research having the potential for causing significant coercive harm to animal subjects with the goal of providing human benefit.²³ Specific aspects of the current BD/EID research context appear to add complexity and particular moral salience to this familiar problem of animal use justification in research. We will address, in turn, problems of justification in: BD-only research uses of animals in comparison with EID and BD/EID research; animal research aimed at MCMs for US Government stockpiling; and the implications of the Animal Rule for BD/EID research.

i) Biodefense animal use justification

Although BD and EID research are currently combined in US NIAID Regional Centers of Excellence and other post-9/11 funding mechanisms, these types of research traditionally have been regarded as distinct. BD research is focused on responding to threat of attack by criminal, state, or terrorist agents, the magnitude and form of which are matters for forward-looking prediction.²⁴ EIDs, in contrast, are naturally occurring, and have specific historical patterns of outbreak and outcomes in terms of human morbidity and mortality that may help to predict future patterns of human impact. Thus, EID research has more clearly definable potential for yielding public health benefit, while

²³ We specify ‘coercive’ harm in this full statement of the *general* type of animal research at issue since even in human research some risk of subject harm is permissible under certain conditions, including consent or assent. Such conditions may be possible to re-create in certain types of animal experiments (see Walker, 2006). In subsequent references to the general type of animal research at issue we may refer only to ‘harm’ or ‘potential harm’ but the full description is always as stated here unless specifically stated otherwise.

²⁴ There have only been two successful bioterror attacks in the United States (King, 2005): one from an internal religious sect (the Rajneeshees) in 1984, and the anthrax attacks of September and October, 2001. James Martin (2006) offers a comprehensive overview of these and other historical uses of biological weapons.

the potential for products of BD research to ameliorate human suffering is harder to predict, but potentially quite high. In practice, however, much of the focus of EID research within combined BD/EID programs is on pathogens that have relatively less extensive human impact from natural outbreak (though still devastating for those affected).²⁵ The priority EID pathogens are selected instead for their potential for bioweapons use (NIH NIAID, 2008 May 12).

In both domestic and international policy and regulatory statements, animal use in biomedical research is usually justified by broad appeal to potential for human (and sometimes animal) benefit.²⁶ In BD research, the need for successful products of animal research, such as vaccines, therapeutics, and diagnostic tools, often takes on a sense of urgency, as bioterrorism is portrayed as a looming threat with potentially catastrophic levels of attending human harm.²⁷ The justification for this type of research by appeal to potential human benefit consequently appears reasonable. Yet the appeal is not as straightforward as it seems.

Since the justification for the use of animals in research is positioned as contribution to human benefit or amelioration of harm, whether or not animal use in the development of BD MCMs is justified would depend on the likelihood and nature of an actual bioweapons use event. For example, if animals are used in the development of a smallpox vaccine, but smallpox is never used as a bioweapon, according to the logic of

²⁵ The 2008 RCE Program Evaluation details the relative focus of all RCEs on all category A-C priority pathogens (Concept Systems Inc., 2008, pp. 18-19).

²⁶ See, for example, the Introduction and Preamble to CIOMS *International guiding principles for biomedical research involving animals* (CIOMS, 1985); *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1996, p. 1); *US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (US OLAW, 2002 Aug 1). Sometimes appeal is also made to the potential for animal benefit. If the “one medicine” movement, which aims to bring human and veterinary medicine closer together again, is successful, perhaps the appeal to benefits for both humans and animals will become more prevalent.

²⁷ See, for example the Center for Biosecurity, UPMC letter to Senator Richard Burr (O’Toole, 2008).

the justification offered, it would appear, retrospectively at least, that the animal use was not in fact justified.

Thus, in order to make a plausible prospective case for the justification of a particular use of animals in BD basic research or MCM development we would need, on this way of thinking, to say something about the likelihood of a relevant bioweapons use. However, both whether, and in what possible form, an attack might occur depends on the intentional actions of human agents. The point is not that it is impossible to speculate about these likelihoods. Indeed, doing just that, in as scientific a manner as possible, is a key part of national security.²⁸ Our point is rather to note that in the area of bioweapons research, the justification for animal use, if it relies on the supposition of later human benefit, depends on events that are themselves dependent on specific intentional human actions. Assessing the likelihood of these kinds of events is, at the very least, quite different from assessing the likelihood and type of a naturally occurring outbreak of an EID.

Is this justificatory issue similar to the problem that all basic science or “exploratory” biomedical research faces? Basic science research causing significant harm to animals is often criticized when it is not clear that it will lead to any promising medical interventions for defined human problems within a reasonable time frame. Arguably, this was part of the source of moral outrage behind the Silver Springs Monkey case, in which nonhuman primates were subjects in basic science head injury studies (Sideris et al., 1999, p. 11), and in the recent ban on primate research at the University of Bremen in Germany by regional authorities (Schiermeier, 2008).

²⁸ The recent US Congress report, “World at Risk” by the Commission for the Prevention of Weapons of Mass Destruction Proliferation and Terrorism predicts a bioterror attack by 2013 (Graham et al., 2008, p. xv).

It seems appropriate that basic science research generally be subjected to more scrutiny the further removed from eventual human benefit it appears, on the one hand, and the more animal harm is involved, on the other. However, we would like to note one seemingly significant difference between the justification for animal use in basic science research more generally and in BD research, basic or applied. The problem for basic science research more generally lies in whether or not it will lead to an eventual application in a “bedside” product. The problem with justifying BD research animal uses is that, even if the animal use is essential to the development of a successful MCM product, it may still never contribute to human benefit. Whether or not it does so depends on whether the product is ever used, which depends in turn on whether, and in what form, a bioweapon against which the MCM is effective is ever deployed.

We think it noteworthy in light of this discussion that BD researchers appear to be moving toward reconceiving BD research for potential contributions to human benefit regardless of bioweapons deployment. For example, research on animal model immune system responses to pathogens, like anthrax or smallpox, is also put forward as generally contributing to knowledge of immune system responses relevant to other infectious disease agents. The impetus for this is no doubt the hope of greater contribution to human well-being. In addition, however, a trend away from BD- *only* research may also be a trend toward greater justificatory stability.

ii) *BD, EID, and distributive justice*

Distributive justice concerns about BD/EID research arise in at least three different areas. For products of BD research placed in the Strategic National Stockpile

(SNS), there are ethical questions about how these products are to be distributed in case of a bioterror attack in the US or an EID event. These questions include how vulnerable populations are protected and to what extent they are given treatment or other priority. These questions have been widely recognized as in need of attention.²⁹ Another important distributive justice question arises with respect to how research funding and other infrastructure resources should be distributed between BD and EID focuses of research, and between these and other types of biomedical research.³⁰ Some have suggested that BD research will also serve a “dual role” of enhancing other public health infrastructures and technological resources; others are concerned that massive appropriations for BD research could undercut research on EIDs that are not likely candidates for use as bioweapons, but have significant public health risk.³¹

The distributive justice issue perhaps most significant for the justification of the use of animals in BD/EID research, however, is that there may be more immediate human needs that could be met by distributing some products of BD/EID research elsewhere around the world than by placing them in the US SNS. Similarly, sharing technologies resulting from BD/EID research with developing nations and avoiding prohibitive technology licensing are also important in improving human welfare where need is greatest.³² If we take seriously the idea that the use of animals in biomedical research is

²⁹ See, for example the Bellagio Statement of Principles regarding disadvantaged groups and influenza planning and response (Bellagio Group, 2006).

³⁰ For example, the now-suspended “Sunshine Project” clearly considered the trend since 2001 to channel funds toward BD research and away from more “traditional” EID research to constitute a justice problem (Sunshine Project, 2005).

³¹ For a discussion of these points see King (2005, pp. 434-5) and Green (2005, p. 130).

³² For a helpful discussion of the various strategies that university technology transfer offices might use in improving access to medicine and vaccines in developing countries see Nelson (2003). We recognize that the issue of how to improve access to vaccines and medicines in developing countries is highly complex. For example, in creating incentives for drug industries to focus on “neglected” infectious diseases, efforts to expand and enrich the viability of markets for these products may be more important than reducing the

justified by the yields in terms of human benefit or amelioration of human harm, this implies that opportunities to provide such benefit or ameliorate such harm should also be taken very seriously. Thus, if the opportunity for benefit arises and is neglected, then quite apart from questions of *humanitarian* obligations, it appears that the need to justify the use of animals by concrete manifestations of human benefit is not properly heeded.

As with the move away from BD-only research noted above, it is significant that the issue of how to improve access to needed vaccines and medicines such as some products developed through BD/EID research has gained ground. For example, in a 2007 statement, “Nine Points to Consider in Licensing University Technology,” sponsored by the Association of University Technology Managers (AUTM), with 69 international institutional signatories (as of 6/16/09), it is recognized that “responsible licensing includes consideration of the needs of people in developing countries and members of other underserved populations” and that “Universities should strive to construct licensing arrangements in ways that ensure that these underprivileged populations have low- or no-cost access to adequate quantities of these medical innovations.” (California Institute of Technology et al., 2007; Association of University Technology Managers, n.d.) While we think it likely in this case as well that the motive for that shift is *humanitarian*, it is also true that this trend gives greater plausibility to the professed research enterprise justification for animal use based on human benefit.

cost of research and development (Webber & Kremer, 2001). Thus, the very government stockpiles that undermine the distribution of medicines and vaccines to where they are most needed, may also serve as an incentive to develop the products in the first place.

iii) *Animal Rule*

BD/EID research to develop MCMs faces an additional challenge: the products that the research aims to develop also usually cannot be tested for efficacy in human beings, for reasons both ethical and practical. Likely bioweapons are precisely those that cause the greatest human suffering and death rates. There is wide agreement that it is immoral to deliberately infect human subjects with these agents.³³ In the case of BD threats that are also EIDs, there may be some possible opportunities for field studies, but these may be practically impossible for a variety of reasons, including small numbers of infected persons, the sporadic nature of the outbreaks, and social factors such as remoteness to transportation networks or the availability of health care facilities (Warfield et al., 2006).³⁴ This adds a challenge to the justification of animal use: in much BD/EID research, the harms arising from research participation are so great that human experimentation would be unethical *even if* participants were well-informed volunteers. Yet it is in precisely this context that animal use may be most extensive and intensive.

The Animal Rule, sometimes called the “animal efficacy rule” or the “two animal rule,” was published by the FDA in the Federal Register on May 31, 2002 (US FDA, 2002) and became effective July 1 of that year. The Animal Rule is codified at 21 CFR Part 314 Subpart I (2009) for drugs and at 21 CFR Part 601 Subpart H (2009) for biologics (US FDA, 2009 a&b). The Animal Rule “provides for approval of certain new drug and biological products based on animal data when adequate and well-controlled efficacy studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or

³³ Nevertheless history is replete with just such experiments, often state sponsored. Martin (2006) offers a brief summary.

³⁴ See also Jester, Tilden, Whitley, & Sullender (2006).

organism to healthy human volunteers and field trials are not feasible prior to approval.” (US FDA, 2002, p. 37989) The rule, an amendment to FDA’s new drug and biological product regulations, was first proposed in the Federal Register on October 5, 1999, as one of a series of amendments designed to accelerate the approval and thus the clinical availability of drugs and biologics for human use. The proposed rule was apparently not specifically conceived as facilitating bioterrorism defense and countermeasures, and very few comments about it were received during the comment period. However, publication of the final rule in early 2002 suggests that the rule’s importance in biodefense became apparent after 9/11 and the anthrax attacks. The proposed rule included requirements that the product be expected to be better than existing treatments; the final rule eliminated this requirement as inconsistent with the perceived “need for a wide range of therapeutic options” (US FDA, 2002, p. 37990).

Importantly, the Animal Rule, addresses only efficacy testing of investigational drugs and biologics. Safety testing must still be conducted in human volunteers, according to the existing regulatory scheme, in order to secure FDA approval. Moreover, the Rule does not bypass clinical efficacy testing in humans; instead, it treats use of the product in response to an exposure as a clinical trial from which essential data will be gathered.

In brief, the Animal Rule applies *only* when it would be unethical to deliberately expose healthy human volunteers in definitive human efficacy studies of agents being studied for their potential to ameliorate or prevent “serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances,” and when it is not feasible to undertake field

efficacy trials “after an accidental or hostile exposure.” (US FDA 2009a&b, 21 CFR 314.600 and 601.90). If a product can be approved based on existing efficacy standards, including accelerated approval using surrogate markers, the Animal Rule cannot be used. The Rule provides that FDA “may” approve a product for which safety has been established, “based on adequate and well-controlled animal studies” establishing that the product is reasonably likely to produce clinical benefit in humans (US FDA 2009a&b, 21 CFR 314.610(a) and 601.91(a)). It specifies that animal studies will be relied on only when four essential criteria are met: 1) “there is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product”, 2) that effect is shown “in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans”, 3) the animal study endpoint is clearly related to the desired human benefit, “generally the enhancement of survival or the prevention of major morbidity,” and 4) the data allow selection of an effective human dose (US FDA 2009a&b, 21 CFR 314.610(a) and 601.91(a)). A plan for “postmarketing studies” – that is, use of the approved product in the field if and when an outbreak occurs – is also required (US FDA 2009a&b, 21 CFR 314.60(b)(1) and 601.91(b)(1)), as is provision of information to “patient recipients” explaining that efficacy has not been tested in humans (US FDA 2009a&b, 21 CFR 314.60(b)(3) and 601.91(b)(3)).

All clinical safety and efficacy testing of new products, whether or not the Animal Rule is used, must be preceded by pharmacokinetic, toxicology, bioavailability and other studies to establish a knowledge base about the product and justify going forward. Such

studies often involve animals, and the use of the Animal Rule does not shortcut any of these studies. FDA also emphasizes that it is no simple matter to meet the Rule's four criteria, and strongly urges that those wishing to use the Animal Rule seek early consultation. As Gronvall, Trent et al. (2007) point out, "more information must be known about the animal model itself, the mechanism and course of disease and the mechanism of the countermeasure than when efficacy studies can be performed in humans" (p. 1085). Roberts & McCune (2008) elaborate by describing in detail 6 key characteristics in the development of animal models capable of satisfying the requirements of the Animal Rule: the nature of the etiologic agent and its disease mechanism in animals and humans; response to the agent; the natural history of the disease or condition; the identification and timing of the trigger for intervention; extensive characterization of the medical intervention, that is, the product being tested; and design considerations leading to a "robust" assessment of efficacy.

Gronvall, Trent et al. (2007) note that the Animal Rule has resulted in very few product approvals, and call for more specific and detailed guidance from the FDA regarding implementation of the rule. Importantly, more extensive use of animals might be necessary in BD research than in EID research, because many potential bioterrorism threats have no well-characterized animal models, "requiring investigators to develop, test and validate animal models, in addition to determining the efficacy and optimal dose of their countermeasures" (Gronvall, Trent, et al, 2007, p. 1085). Presumably, EID threats, by their very nature, are at least somewhat less likely to lack for animal models.

Regardless, however, of the nature of the threat under investigation, as Gronvall, Trent et al. and others have noted, animal models are rapidly being developed and refined. Investigators eager to make progress against significant threats, whether those threats are deliberate or accidental, will be testing novel products using the Animal Rule in increasing numbers. Calls for improved guidance from FDA are mounting, since investigators rightly recognize that without better guidance, they could complete extensive animal studies and ultimately be told by FDA that the Animal Rule cannot be used, or that the data they have gathered cannot be applied to its use. In response to these urgent requests, in September 2008, FDA's Center for Drug Evaluation and Research produced a "concept paper" —a draft document preliminary to a guidance document—titled "Animal Models: Essential Elements to Address Efficacy Under the Animal Rule." The concept paper noted: "The number of animals available for research, especially nonhuman primates (NHP), is finite. The animal efficacy studies conducted under the Animal Rule will use a significant number of animals." (US FDA, 2008, p. 3).

More recently, Draft Guidance with the same title as the concept paper, and nearly identical content, was issued by FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Its availability was announced in the Federal Register on January 21, 2009, with a comment period extending to March 23 (US FDA, 2009c). No final guidance document has yet been announced —which is far from unusual for such documents. Three aspects of the guidance are noteworthy for our purposes. First, throughout its 16 pages, it repeatedly recommends that sponsors contact FDA early and frequently, emphasizing the availability and desirability of review and feedback and even promising the possibility of review under Special Protocol

Assessment provisions, which specify in advance the conditions of product approval (US FDA, 2009c, p. 15). This emphasis seems clearly directed toward reassuring sponsors (and, thereby, investigators) that more specific and detailed guidance is available through direct communication with FDA. Second, the guidance delineates clearly what it does *not* address, including “the threshold for determining that human efficacy studies are not ethical and/or not feasible” (US FDA, 2009c, p. 4). Finally, the concept paper’s acknowledgement that the number of animals available for research is finite, and that the Animal Rule “will” use a significant number of animals, has been changed in the draft guidance to the following: “The animal efficacy studies conducted to support approval under the Animal Rule are likely to use a significant number of animals.” (U. S. FDA, 2009c, p. 7) It is not apparent whether this more qualified statement is intended to signal increased awareness of the need to remain cognizant of the 3Rs, such that FDA, in consultation with a sponsor, anticipates addressing ways to reduce the use of animals in a given application of the Animal Rule, or whether it is simply a rhetorical measure employed to downplay concerns about the heightened use of animals in this research context.

Finally, the development of animal models for BD/EID research poses additional ethical challenges for animal researchers, for several reasons. First, animal models are never perfect, so that researchers must be prepared to address unanticipated degrees of harm to animal subjects when attempting to gather data of relevance to human disease. Second, in BD-only research in particular, testing involving unprecedented bioweapons (e.g., known pathogens with increased virulence or synthetic pathogens) could pose unprecedented risks of harm to animal subjects. And third, the need to balance the

gathering of useful data from animals with the requirement to minimize animal suffering may pose especially difficult tradeoffs when using the Animal Rule in the context of BD/EID research, including, but not limited to, the need to identify suffering in subjects who cannot articulate their complaints and the need to devise means to reduce suffering in subjects who cannot comply with instructions (e.g., by adapting the use of analgesic for mouth sores, which can be accompanied, for human subjects with instructions like “swish but don’t swallow,” in ways better suited for subjects unable to comply with such instructions).

It could reasonably be argued, therefore, that the Animal Rule might increase the amount of research with animals and might alter the nature of the research in which animals are used, depending on the interventions for which countermeasures are sought. Thus, the Animal Rule has implications for the justification of animal research. We turn now to an examination of key philosophical issues relevant to the justification of animal research by appeal to human benefit. Following this, we return to a tension between the Animal Rule and the common internal ethical framework for the assessment of animal research, the 3Rs, in light of this philosophical discussion.

iv) Consequentialism, utilitarianism, and animal use justification

As we have seen, the practical ethical questions that arise for BD and/or combined BD/EID research include the relevant potential of BD research animal uses to promote human benefit and the relationship between the appeal to human benefit as a justification in theory and actual dedication to the promotion of human benefit through product and technology sharing in practice. The appeal to human benefit cannot, however, serve as an

adequate justification for harm-causing animal use without further discussion and analysis.

The appeal to human benefit as a justification for animal use in research is consequence-based, or consequentialist. The consequence appealed to, human benefit, justifies the harm that is done to animals in pursuit of that benefit. However, for an adequate consequentialist moral justification we need to offer more than a vague appeal to human benefit; instead, the end of human benefit must be somehow established as an appropriate trade for the relevant animal harm. But in establishing the appropriateness of the trade, we need to say something about what kinds of harms can (morally) be traded for what kinds of goods—including appropriate magnitudes and probabilities. We need to know, specifically, what *nature and magnitude of certain* animal harm is justified by what *nature, magnitude, and probability* of human benefit. If we do not know this, we cannot say with any specificity which types of animal uses are justified.

Interestingly, however, the US regulations guiding animal care and use in research offer no such guidance regarding permissible tradeoffs between animal harm and sought-for human benefit. Indeed, there is no definite requirement to weigh proposed human benefit against animal harm at all.³⁵ In principle, though not necessarily in practice, even the most minor and improbable of human benefits could be thought to justify even the most serious of harm to animals. By contrast, comparing animal harm

³⁵In contrast, US human subjects research regulations require the balancing of risks of harm to subjects against potential benefits to society—even though little guidance is provided as to how to accomplish this. (Protection of Human Subjects, 2005, 45 US CFR § 111.a.2)

and sought human benefit is part of many European countries' research review processes, though how these comparisons function in practice is not as clear (Smith et al., 2007).³⁶

If no consideration of the appropriateness of the trade between animal harm and human benefit is seen as necessary, then the appeal to human benefit does not serve as a moral *justification* for animal use at all. Rather, it might be merely a factual or predictive statement about which sorts of good things for humans might follow from which sorts of animal uses. In fact, it is not clear that the appeals to human benefit within the regulatory guidelines either in the US or internationally (CIOMS, 1985) actually are meant as justifications for animal use. For example, the US Principles statement is as follows:

“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.” (NIH OLAW, 2002 Aug 1) Clearly, this statement could simply be a factual claim, not an attempt to justify needed animal experimentation at all.

However, if the appeal to benefit is *not* meant as a justification for animal use, then it is not clear what justification there could possibly be. No other justification is ever offered, and it is hard to imagine a non-consequentialist justification for such use. One possible response is that *no* justification for animal use is needed. However, it is important to be clear about what this would mean for the moral significance of animals. If

³⁶ In a November 2008 Proposal for a Directive of the European Parliament and Council on the Protection of Animals Used for Scientific Purposes (hereafter “Proposal”), the European Commission called for mandated independent ethical and scientific review of proposed projects including balancing expected benefits to humans against harms to animals (European Commission, 2008, articles 37 & 38, p. 18). The Commission also called for an upper limit to allowable animal pain and distress (European Commission, 2008, article 22, p. 16). The European Parliament has subsequently voted on these and other recommendations of the Commission. We have not been able to review any primary documents regarding the May 2009 vote results, however, it has been reported that the mandate for independent ethical and scientific review was rejected while setting an upper limit on pain and distress was accepted (Humane Society International, 2009 May 9). For further discussion of the European Commission’s 2008 Proposal see footnotes 44, 46 and 47 and pp. 59-60 below.

no justification is needed for harm-causing uses of animals in the pursuit of human benefit, then it would follow that the animals so used would not have any direct moral significance. We would not be required to treat them well for the sake of their own well-being, but because how we treat them is significant in some way for our treatment of each other, for example through the development and expression of good character or through respect for one another's personal attachments to animals (such as pets).³⁷

This is arguably a philosophically dubious position; more importantly for our purposes here, however, it is a position that seems in conflict with the general spirit and specific requirements of the US regulations guiding animal care and use, with the practices and attitudes of animal researchers, and with the views of IACUCs (not to mention the general public). On the contrary, an assumption that animal welfare is to be promoted and harm minimized *for the sake of the animals themselves* seems to be the most plausible interpretation, not only of the general ethos of responsible conduct of research with animals, but also of many of the particular requirements guiding animal research: to minimize pain wherever feasible, to reduce numbers of animals used to those necessary for the research, and to kill animals painlessly, just to give a few examples. Indeed, the very term "sacrifice," used by animal research scientists to describe the killing of research animals, implies that animals are themselves morally

³⁷ This is a standard interpretation of Immanuel Kant's view about our moral obligations toward animals. For an expression of his view that seems in keeping with this interpretation see his *Lectures on Ethics* (2001, 27/710, p. 434). For a more nuanced interpretation of Kant's view on animals and nature in general see Wood (1998). A version of this view is also supported by Carruthers (1992). Carruthers argues that the proper manifestation of the virtue of sympathy in this indirect treatment of animals requires that we treat them well for their own sakes (1992, p. 157). This is not very plausible, however, since he also argues that we have no trouble morally distinguishing human from non-human animals in our treatment of them (1992, p. 115); thus it is unclear why the appropriate virtues toward animals would require treating them well for their own sakes when they do not, on his view, have any direct moral significance.

valuable and that their deaths for the sake of the research ends are unfortunate, if necessary.

If animal well-being should be promoted for the sake of the animals themselves (that is, animals are themselves *morally considerable*), and the appeal to human benefit is meant as a justification for animal use, we need some more specific guidelines about the permissible trade-offs between animal and human well-being in the pursuit of specific scientific aims. The philosophical view most relevant to consequence-based justifications for actions is utilitarianism. On a utilitarian model, morally right actions are those that lead to the greatest overall welfare. However, this view also requires that we give equal consideration to all similar welfare (or interests) regardless of where or in whom such interests inhere. Thus, since many animals have welfare of the relevant types (pleasures and pains, for example), we would need to give equal weight to comparable human and animal welfare. This does not mean that we would have to weigh all human and animal suffering equally, since much of it is not in fact equal, but it does mean that where the suffering (or welfare) is comparable, it would have to be weighed on a “fair scale” without regard to the species of the individual in which it occurred. Peter Singer, a pioneer proponent of this type of approach to animal welfare in the modern animal research context, concludes that much animal research now being conducted is not justifiable.³⁸

If this sort of radical equality between like human and non-human animal interests is rejected, then perhaps one might turn to a discounted consideration of animal interests. That is, the weight or significance given to animal interests in comparison with human interests would be discounted, even where the interests themselves were otherwise

³⁸ See, for example, his discussion in *Practical Ethics* (Singer, 1993, pp. 65-8).

comparable.³⁹ On a model like this one would still need to: 1) Justify, or at least reach some reasonable agreement about, the appropriate discounting of otherwise comparable animal interests and 2) Give a specification of this discounting in practice.

Importantly, the fundamental question of what weight or significance should be placed on animal, in comparison with human, welfare is not the only question of significance for a utilitarian approach to permissible harm-benefit trade offs. Also significant are the probability, duration, and temporal remoteness of any benefits and harms as well as how the benefits and harms are related.⁴⁰ Practically, then, in taking this kind of approach to the question of what animal research is justified we would need to consider, in addition to how much to discount animal interests, the probability, magnitude, and time frame for human benefit in comparison with the magnitude and duration of certain or predicted animal harm.

It is clear, at a practical level, why neither US regulatory guidelines nor scientists involved in animal research would want to offer anything more than a vague appeal to human benefit as a justification for animal uses in research. Providing a clearer statement of what kinds of trade-offs between animal and human wellbeing are justified would very probably undermine the moral validity of some types of research currently conducted. Moreover, it is, to understate in the extreme, not the simplest of philosophical tasks. Even where trade-offs between animal and human wellbeing are explicitly considered (for example, as already mentioned, in the ethical review processes in many EU countries), which trade-offs are considered permissible may vary widely or simply remain

³⁹ This model would be somewhat similar to the two-tiered moral status view discussed in Warren (2000, pp. 85-88) or the discussion by Brody (2001) of discounting somewhat animal interests relative to human interests.

⁴⁰ Jeremy Bentham, the founding father of utilitarianism discusses how to measure the value of pleasures and pains in *The Principles of Morals and Legislation* (1988, pp. 29-32).

unspecified.⁴¹

Although practically wise ethical judgment requires context sensitivity and therefore cannot rely on a single decision algorithm of permissible trade-offs between animal harms and human benefits, as long as the justification for animal research is essentially human benefit, there remains a need to address, in a general sense, the component elements and relative significance of such permissible trade-offs. In absence of any discussion of permissible trade-offs between animal harms and proposed human benefits, US regulations and practices appear incoherent. On the one hand, animals appear to have direct moral significance (their welfare matters because *they* matter); but on the other hand, any use for any type of human benefit appears, in principle, justified—in which case animals cannot in fact have any direct moral value.

v) *Animal Rule and the 3Rs of animal research*

The philosophical problem of animal research justification is further complicated in the context of BD/EID research by the interpretation and application of the 3Rs—the ethical framework most widely adopted by animal research communities. The 3Rs of animal research -- Replacement, Reduction, and Refinement – appear to assume that animals are morally considerable and that therefore, though their use in research is justifiable, it should be minimized in appropriate ways. Yet the 3Rs themselves may not

⁴¹ The FELASA Working Group survey of European Union member countries the ethical review processes of those countries that weigh benefit and harm in animal research, and demonstrated variability therein that could affect both what is considered in such evaluations and how the factors considered are balanced. For example, differences were identified in the level of science practice assessed (project, protocol, procedure), the type of ethical review (from single person local review to national committee review), and whether any specific guidelines for review are mandated (Smith et al., 2007). The working group offered a helpful and fairly comprehensive summary of the kinds of benefits and harms that should be considered in ethical review of a proposed use of animals (*Ibid*, p. 16), but did not consider the fundamental issue of the relative value of harms to animals as compared with potential human benefit.

be sufficiently clear in theory, leading to complications in practice. In this section we specify how these complexities play out with respect to the Animal Rule.

The 3 Rs were originally formulated by W. Russell and R. Burch in their 1959 book *The Principles of Humane Experimental Technique* (Russell & Burch, 1959). Today these principles (or aims)⁴² are widely embraced by animal research communities and in regulations in the US and international arenas governing animal research. The aim of replacement calls for the “absolute” or “relative” replacement of animal subjects with other study means. Absolute replacement might be through computer modeling or reliance on human volunteers. Relative replacement refers to the use of animal tissue or cells in vitro, as opposed to in vivo use of animal subjects. The aim of reduction calls for the numbers of animals used to be the fewest needed for the scientific study aims. Reduction may also be interpreted to require fewer duplicate studies and high standards for original study design (to avoid wasteful animal use). The aim of refining animal use has two elements. First, the least invasive and least painful procedures to get the required data ought to be used. The second element considers whether “lower” animal species may be used.

Despite widespread agreement on the 3Rs in the animal research science community, this framework is not without tensions, both in terms of relative emphasis between the Rs and between the promotion of the 3Rs and other interests. Public emphasis has sometimes been put on the replacement of animals over the other two

⁴² It matters quite a bit whether we think of these as (morally required) principles of research or as (morally salutatory) aims of research. However, this distinction is not apparent as such in the US regulations guiding research. We discuss the particular interpretation in the US PHS principles in more detail below.

aims.⁴³ At the same time, it is recognized by those attuned to animal experimental practices that proper selection of methods to minimize pain, humane study endpoints, and avoidance of study duplication are just a few elements of refinement and reduction that are both significant for animal welfare and not currently fully implemented.⁴⁴ Experts in the field of animal alternatives are also concerned that the 3Rs are simply not taken seriously enough in practice, in particular when the implementation of these principles is in tension with other interests or practices.⁴⁵ While we think the issues of relative emphasis among the Rs and the practical emphasis put on implementing the 3Rs are important, we also think that there is a deeper theoretical shortcoming with the 3Rs framework itself. This is highlighted by considering the relationship between the 3Rs and the Animal Rule in light of our discussion about the consequentialist justification of animal research.

When we evaluate the Animal Rule in light of the 3Rs, the widely held set of norms of the animal research science community and governing regulations, we can identify several *prima facie* tensions. First, the Animal Rule requires that study results be

⁴³ For a brief discussion of the relative popular significance placed on each of the 3Rs see Smith (2001). The European Centre for the Validation of Alternative Methods (ECVAM) established through Directive 86/609/EEC (the European Union directive on the protection of animals used for experimental and other scientific purposes), focuses on replacing animals over reduction or refinement. In particular their mission is, “To promote the scientific and regulatory acceptance of non-animal tests...” (ECVAM, n.d.). In some contrast, the Johns Hopkins University Center for Alternatives to Animal Testing (CAAT), defines “alternatives” in its mission statement as applying to each of the 3rs (Johns Hopkins University CAAT, 2009).

⁴⁴ For example, the European Commission offers recommendations regarding each of these factors in its November 2008 Proposal (European Commission, 2008, articles 12,13, 41, pp. 15, 19). For a helpful discussion of the need for humane endpoints in toxicity and vaccine testing see Stokes (2002).

⁴⁵ A particularly salient example of this is Michael Balls, former head of the ECVAM, who has written that there is a “failure of governments to actively apply legislation requiring the discontinuation of animal test procedures when scientifically satisfactory alternative methods become available.” (Balls, 2002) Alan Goldberg, former head of CAAT, discusses a greater emphasis on the 3Rs in Europe as opposed to the United States and a concern that US scientists are simply not properly educated in the practical implementation of the 3Rs in a 2004 Fund for the Replacement of Animals in Medical Experiments (FRAME) lecture (Goldberg, 2004, pp. 8-10).

duplicated in two animal species (or one well suited to human extrapolation), which is in tension with the goal of reducing the numbers of animals used by not duplicating study results. Secondly, the Animal Rule requires the in vivo use of animals, which is in tension with the aim of replacing animals with other study methods. Perhaps of most significance, however, the Animal Rule requires, in effect, death or major morbidity as study endpoints, which is in tension with the aim of refining animal use. Also in tension with the aim of refining animal use, the Animal Rule specifically allows for the use of animals most suited to human extrapolation as an alternative to the use of two species, which, in effect, provides impetus for greater non-human primate use.

Why, then, if there is so much apparent tension between the Animal Rule and the 3Rs, is the Rule nevertheless in keeping with regulations governing animal care and use? The reason for this is that the 3Rs may be given both more and less demanding interpretations, both in their content and in their status as moral claims. For example, the content of the requirement to reduce animal use might, in the weak interpretation, require only that numbers of animals used in a protocol not exceed numbers needed for the scientific aims. No animal researcher has good reason to use more animals than needed for her aims and has, moreover, strong prudential reasons not to do so. In the stronger interpretation, however, the requirement to reduce animal use might imply that only those studies most promising for contribution to human benefit ought to be done, and that results and study methods should be widely shared across institutions or companies to reduce any duplicative studies. Similarly, the call for reduction might be a moral requirement or principle, which may be overridden only in special circumstances and not

for mere practical convenience. Or it might be viewed as a salutatory, but not required, moral aim.

OLAW interpretation of the 3Rs, as reflected in the Principles for Care and Use, is on the weak side. With regard to reduction of animal use, the principles state that “the animals selected for a procedure should be...*the minimum required to obtain valid results* (emphasis added),” thus giving the least demanding interpretation in terms of content (though *requiring* that the standard is met). For replacement, the principle states, “Methods such as mathematical models, computer simulation, and *in vitro* biological systems should be *considered* [second emphasis added],” thus giving replacement the status of an aim rather than a requirement. The interpretation of refinement occurs in several places, but one key statement is: “Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain, *when consistent with sound scientific practices*, is imperative.” (NIH OLAW, 2002 Aug 1) This interpretation presents refinement as a requirement (indeed an imperative), but since it is a requirement secondary to science aims, it is not a *moral* requirement of any ordinary sort.

vi) *BD/EID justification for animal use conclusion*

A consequentialist justification for actions or practices can only be employed where we can make reasonable predictions about the potential for benefit and harm resulting from our actions or practices and where we can offer at least some sort of framework for comparing likely harms and benefits. Furthermore, the appeal to human benefit in justifying animal use puts a (defeasible) burden on us, independent of

humanitarian aims, to promote human benefit in the use and sharing of MCM gains made through animal use.

It is important to emphasize that we do not actually think that a justification of animal use can rely on a simple formula for weighing animal against human interests. As we have already mentioned, any morally useful “weighing” of this sort should be both context-sensitive and dependent on the kind of harm to animals, the type of animal, the probability of human benefit, the type of human benefit, etc. Nor do we think that every type of animal harm can necessarily be offset by human benefit. Perhaps some animals should not be used for harmful experiments at all, or some experiments might be so burdensome that no benefit would outweigh the harm involved.⁴⁶ In some tension with these ideas is the concern that some human needs might be so important that any experiment could be justified to meet them.⁴⁷ In other words, at best, a consideration of how to trade off human and animal interests is just one part of a larger picture of the moral justification of animal use in biomedical experimentation. Still, as long as the appeal to human benefit serves as the apparent justification for animal use, it does not seem justifiable to fail entirely to measure harm to animals against proposed human benefit -- unless we view animals as *themselves* morally inconsiderable.

We have seen that if the appeal to human benefit can be a justification for animal use at all, it must offer more specific guidance about permissible trade-offs between

⁴⁶The European Commission’s November 2008 Proposal suggests both of these conclusions in its call for a near total ban on invasive experimentation on great apes (but see footnote 47 and the discussion on pp. 59-60 below) and, as already discussed above (in footnote 36), setting an upper limit to pain and distress that animals are permitted to experience (European Commission, 2008, articles 17, 22, pp. 15-16).

⁴⁷ It is interesting in this regard to note that the European Commission calls for an exception to the great ape research ban for “action in relation to a life-threatening, debilitating condition endangering human beings [when] no other species or alternative method could suffice” (European Commission, 2008, article 17, p. 15). See also discussion on pp. 59-60 below). However the Commission does not qualify the call for placing an “upper limit” on animal pain and distress (European Commission, 2008, article 22, p. 16). See also footnote 36 above.

animal harm and human benefit. This is of crucial significance for the question of which types of BD/EID uses of animals are justified. Thus far, however, it appears that satisfactory guidance is provided neither by the regulatory apparatus of animal care and use nor by the 3Rs. This situation raises particularly acute moral issues for the use of nonhuman primates in BD/EID research, as we shall address next.

Section B) Increased non-human primate use

In this section, we turn to a discussion of the increased and relatively intensive use of nonhuman primates in BD/EID research. The use of nonhuman primates in biomedical research in general has involved various forms of heightened social, regulatory, and philosophical ethical scrutiny.⁴⁸ BD/EID research has the potential for increasing the use of nonhuman primates as well as intensifying their use (that is, increasing the magnitude and probability of serious harm to them) in research, because of both the nature of BD/EID research and the regulatory mechanisms for MCM product approval (i.e. the Animal Rule). In this section we discuss those factors within BD/EID research and explore the background philosophical ethical issues that undergird moral tensions for BD/EID research using nonhuman primates.

⁴⁸ Consider, for example, social reaction to the Silver Springs monkey use (see p. 14 above), the European Commission's proposed restrictions on NHP use (discussed below on pp. 59-60 and above in footnotes 46 and 47), requirements for psychological welfare considerations in the 1985 amendments to the AWA (US Animal Wellness Information Center, n.d.; US OLAW, 2007 Mar 27), and the philosophical proposal of *The Great Ape Project* that great apes are the moral equals of human persons with rights (Cavalieri & Singer, 1993, pp. 1-3).

i)BD/EID Primate use and demand

Non-human primates (hereafter, NHPs) account for a very small percentage of the animals used in research.⁴⁹ There are some forces moving biomedical research away from the use of NHPs, including the financial and logistical burdens of properly housing and caring for the animals, a broad agreement that animal subjects should be the “lowest” or least complex from among the species appropriate to the study aims, and social pressures, especially in some European Union countries.⁵⁰ Yet despite these forces and low rates of use in research generally, there are two aspects of BD/EID research that, when combined with increased funding, facilities, and other resources put toward this research, may tend in the opposite direction, toward increased demand for and use of NHPs as animal subjects.

The first aspect is common to both EID research and combined BD/EID research. For a number of EID pathogens studied, NHPs are considered scientifically appropriate animal models for human disease. In EID research generally, for example, the use of

⁴⁹ According to a 2004 review of publications discussing NHP use in research generally in 2001, NHP use is estimated at 100-200 thousand animals world-wide, which is approximately 0.1% of animals used in experiments. Of these animals, an estimated 1-2 thousand were terminated in acute studies. Notably, however 50% of use was in the US (Carlsson, Schapiro, Farah, & Hau, 2004).

⁵⁰ These forces are especially salient with respect to the use of Great Apes. A 2007 *Science* piece notes, “fifteen years ago, the United States was one of a half-dozen countries that had captive chimpanzees available to biomedical researchers. Today it stands alone.” (Cohen, 2007, p. 450) Due to the fiscal burden of caring for Chimpanzees over their lifetime, a National Center for Research Resources 1995 temporary moratorium on breeding federally supported chimpanzees is now permanent (NIH National Center for Research Resources, n.d.). In the UK great apes are not used in experiments as a matter of policy, though not of law (Nuffield Council on Bioethics, 2005, p. 52) and in the EU in general no biomedical research on has actually taken place using great apes since 2002 (Vogel, 2008). Further, a near ban on the use of great apes for biomedical procedures in the EU has reached agreement from the European Parliament (see: discussion on pp. 59-60 below; Dr Hadwen Trust for Humane Research press release (2009 May 5); Humane Society International press release (2009 May 9)). Things are somewhat more complex with regard to other primates, where there is substantial tension between some scientists and animal protection groups regarding their use (Vogel, 2008). In specific cases, the use of primates has been restricted in the EU. For example, a Swiss court revoked the licenses for two neurological experimental programs using macaques (Abbott, 2008). See also pp. 59-60 below regarding the European Commission’s 2008 proposed limits on both great ape and NHP research. In the US, while there are no special limitations on the use of NHPs in biomedical research, the choice of them (or dogs or cats) as an animal model must receive “thorough justification” (NIH OLAW, 2009, p. 4).

NHPs for HIV/AIDS studies amounted to approximately 6% of all NHP research in 2001 (including non-biomedical research) (Carlsson et al., 2004, p. 231). In combined BD/EID research, NHPs are seen as a crucial resource for the development of drugs and vaccines because of their suitability as models for research with a variety of priority pathogens.⁵¹

The second aspect of research that highlights the scientific appropriateness of NHPs for study of priority pathogens is research in which efficacy studies in humans are not ethical or feasible—that is, research conducted according to the FDA’s Animal Rule, as detailed above (U.S FDA, 2009a&b).⁵² The Animal Rule promotes the highly intensive use of NHPs. Indeed, as one researcher puts it, “The FDA would prefer that one of the animal models [for MCM efficacy assessment] be a nonhuman primate.” (Jean L. Patterson interview, from Drexler, 2007, p. 99)

In BD/EID research, then, the suitability of NHPs as animal models for the human diseases studied, combined with moral and practical limitations on the use of human subjects for testing vaccine or drug efficacy, effectively promotes NHP use. When the large increases in funding, facilities and other resources directed toward BD/EID research are added to these factors, it is clear that “the demand for nonhuman primates will undoubtedly increase to meet biomedical needs in this current age of biodefense” (Patterson & Carrion, 2005, p. 15). Whether for these or other reasons, it appears that

⁵¹ For a brief review of the appropriateness of NHP models for various priority pathogens see, Patterson & Carrion (2004). For a thorough review of the relevance of NHP models to biodefense research by pathogen type see Swearingen (2006, pp. 86-88; 7-98; 123-28; 153-155; 168; 173-175; 189-193; 196; 198-201; 208-223; 233-236; 264-266; 268-270; 282-286; 297-307).

⁵² The Animal Rule is relevant to contexts other than BD/EID research (US FDA 2009c), but has received considerable attention in the BD/EID context, having been used, for example, in FDA approvals of a treatment for nerve gas exposure in 2003 (US FDA, 2003) and a treatment for cyanide poisoning in 2006 (US FDA, 2006).

biomedical research use of NHPs is in fact on the rise, at least in the US.⁵³ In the rest of this section, we focus in more detail on the moral status of NHPs as presenting a problem for the potentially increased and intensive use of these animals in BD/EID research.

ii) *Primate relative moral status*

The evolutionary closeness of human and some NHPs makes NHPs especially appealing subjects for BD/EID research from one point of view, but at the same time calls into close moral attention a core presumption of animal research in general, and of the Animal Rule in particular. The rule provides an approval mechanism for MCMs through the use of animal subjects when it would be impractical *or unethical* to use human subjects, even with their informed and voluntary consent. Effective application of the Animal Rule requires that the animal subjects be similar enough to humans with regard to the particular biological mechanisms under study, for indications not only of effectiveness but also of effective dose extrapolation. Thus the assumption is that, even for animals with such strong biological similarity to humans, it is ethical to do to them what it would absolutely not be ethical to do to humans.

The ethical tension inherent in doing research on animals because they are “like us”, while at the same time being willing to do to them what we are not willing to do to

⁵³ In 2007 the number of NHPs used in “research, experiments, testing, and teaching” was reported by the USDA at 69,990 (US Animal and Plant Health Inspection Service, 2008, p. 13). In 2006, the number reported was 62,315 according to the American Society of Primatologists (2008). Since the 2007 USDA report is the first comprehensive report publicly issued since 2001 it is difficult to tell the precise rates of increase in use. However, the Humane Society of the US reports a 29% increase between 2001 and 2007 (Humane Society of the United States, 2009 Jan 9). They also report, “China is greatly increasing primate use and export and is establishing itself as a global force in the NHP research industry.” (Humane Society of the United States, 2009).

other humans, has long been noted.⁵⁴ What is striking about the Animal Rule is that it calls for the use of animals *most* biologically “like us” and that it specifies study endpoints that are highly likely to involve the suffering and/or death of the animals studied. Thus, it brings this long-recognized ethical tension in animal research to a head.

In the Nuffield report, the strategies for justifying the “use of animals in research where the use of non-consenting human participants would be unacceptable” (Nuffield Council, 2005, p. 38) were presented as 1) Claiming lesser moral status for the animals involved; 2) Arguing that it mattered less to the animals to be used in these ways; or 3) Claiming that the research must be done despite being morally impermissible in a certain sense. The issue we address here, of NHP use in BD/EID research aiming at product approval through the Animal Rule, is different from the issue the Nuffield report addresses, since the corollary human experiments would be unethical *even if* participation were voluntary and informed. Thus, the justification of animal use is perhaps even more difficult. Still, we think the same three options are available. In this section we mainly address the first option, that is, the issue of the moral status of the animals involved, with special focus on the issue of NHP moral status. We also discuss, at the end of this section, whether NHP interests are different enough from human interests to support using them

⁵⁴ An especially poignant example of this tension that occurs in non BD/EID animal research arises in Harry F. Harlow’s psychological studies of maternal deprivation in infant rhesus macaques in the 1950’s. He writes, “The macaque infant differs from the human infant in that the monkey is more mature at birth and grows more rapidly; but the basic responses relating to affection, including nursing, contact, clinging, and even visual and auditory exploration, exhibit no fundamental differences in the two species. Even the development of perception, fear, frustration, and learning capability follows very similar sequences in rhesus monkeys and human children.” (Harlow, 1958, p. 674) Somewhat startling for the reader accustomed to current day ethical norms regarding human subject research, however, is Harlow’s reported reasons for not using human infants for such studies as these are not *moral* reasons, but scientific ones. He writes, “Unfortunately, the human neonate is a limited experimental subject for such researches because of his inadequate motor capabilities. By the time the human infant’s motor responses can be precisely measured, the antecedent determining conditions cannot be defined, having been lost in a jumble and jungle of confounded variables.” (*ibid*) In a sense, then, *for Harlow*, there is no moral tension in the use of macaques because they are “like us”. It is just a matter of the best scientific subject for the study.

where humans cannot be used. We consider the third strategy, which in essence accepts that animal research is not morally justified in one sense but claims that it is the lesser of two evils in some other sense, to be an ethically unstable position.

As we have already described, questions of moral status focus on the level and type of attention that is owed to the interests, well-being, needs, or integrity of a being or other item. In the section above on justification of BD/EID research generally, we mainly focused on the moral considerability of the animal subjects. Here, in the discussion of the justification of BD/EID research using NHPs in keeping with the guidelines offered by the Animal Rule, we focus on the question of *relative* moral status. The issue here, then, is what moral status NHPs, as the animals “most like us”, have relative to human beings.

Biological relatedness does not *necessarily* correlate to relatively similar moral standing. However, given the comparability of some non-human and human primates with regard to a variety of complex social, emotional, and intellectual capacities, a pointed question arises: Can anything other than human prejudice support BD/EID research using the Animal Rule on non-human but not human primates? In his highly influential work *Animal Liberation* (1995, first published 1975), Peter Singer used the term “speciesism” (originally coined by Richard Ryder) as a label for the practice of treating non-human animals as having lesser moral standing simply by virtue of not being members of the human species. More recently, other philosophers have argued specifically for “moral individualism,” or the view that each being should be recognized

as having the moral status that befits its intrinsic moral properties, where these are usually understood as intellectual and emotive (or, loosely, psychological) capacities.⁵⁵

Once one accepts the tenets of moral individualism, the attribution of full moral status to all human beings regardless of whether they manifest specific morally relevant capacities, and the denial of this status to those NHPs with relatively similar (and even, when comparing individuals, sometimes higher) capacities, is clearly speciesism. This is so clear, in fact, that many have assumed it is sufficient simply to point out that not all humans share certain seemingly morally relevant capacities, while many non-human animals do have these same capacities. As a result, the thought seems to be, we will be forced, on pain of contradiction, to extend the same moral consideration to those animals as we do to the human beings at issue. (Note, however, that “same consideration” does not mean “same treatment,” because animals and humans often have different kinds of interests.) This so-called “argument from marginal cases” has played a central role in support of the extension of greater moral consideration to non-human animals.

If we accept the argument from marginal cases (and its roots in moral individualism), then it is clear that the assumption behind the Animal Rule is morally untenable. That is, not only can we *not* assume that it is morally permissible to do to NHPs what it is morally impermissible to do to humans; indeed, in the case—at the very least—of causing severe pain and/or death to those individual animals with the same morally relevant capacities as some humans, it is patently impermissible.

One possible rejoinder is to argue that non-human animals have some, but lesser, moral standing than humans. Another, more promising, route is to argue against the view

⁵⁵ McMahan (2005) argues most specifically and thoroughly for this view. However, it is a view shared in its basic tenets by many philosophers writing on moral status questions, including Rachels (1989) and Tooley (1998), among many others.

that moral standing is based on intrinsic psychological properties of individuals.

However, whichever of these routes is taken, problems remain for the Animal Rule. We shall discuss each option briefly in turn.

Suppose we claim that all animals, or at least those with the capacity for pain sensations, have some moral standing, but that this is in a hierarchy with humans at the top—in other words, moral status varies along a sort of “great chain of being”. This might even be considered the popular view of animal moral standing. There is some evidence in the US regulatory structure guiding research on animals that would indicate support for this view. For example, in 1985, the AWA added requirements that the psychological welfare of NHPs must be given special consideration (AWA of 1966 as Amended, 1996). Further, in 1997, members of the National Research Council’s Committee on Long-Term Care of Chimpanzees concluded that chimpanzees should not be killed for population control purposes (Degrazia, 1999, p. 28).

This kind of view, regarding at least the special moral standing of NHPs, and of great apes specifically, in comparison with other animals, is even more pronounced in some other countries. Citing as general support the “importance attached to animal welfare [as] evolving in terms of ethical concerns [which has] become a “cultural attitude” for European society” (2008, p. 3) and the fact that, in particular, “the use of non-human primates is of the highest concern to the public” (2008, article 16, p. 15) the European Commission called for the use of NHPs in research to be limited to:

[E]ssential biomedical areas for the benefit of human beings for which no other replacement alternative methods are yet available and only in cases where the procedures are carried out in relation to clinical conditions having a substantial impact on patients’ day-to-day functioning as being either life-threatening or debilitating, or for the preservation of the respective non-human primate species. (2008, article 16, p. 15).

The European Commission also proposed banning research on great apes except for

species preservation or when absolutely necessary “in relation to a life-threatening, debilitating condition endangering human beings” (2008, article 17, p. 15). In contrast, however, in a May 2009 vote on the Commission’s report, the European Parliament rejected the position of the Commission on NHPs in general although it did agree to the restrictions on the use of great apes (Animal testing, 2009; UK office of the European Parliament, 2009 May 8; see also footnotes 46 and 47, above). Since no great apes are currently used in biomedical research in the EU (see footnote 50, above) this agreement with the Commission seems more symbolic than substantive.

If one takes this “hierarchy” approach to moral status, two fairly serious problems remain for justifying the use of NHPs in BD/EID research in keeping with the Animal Rule. First, the most plausible reason for supporting such a view would be that morally relevant characteristics of animals vary along this same hierarchy of biological complexity,⁵⁶ but if that is so, we are once again faced with the question of why individual NHPs with the same morally relevant capacities as individual humans (babies, perhaps, or adults with advanced senility) should be subjected to treatment that is morally impermissible for humans. Second, and perhaps of even more specific practical concern, if NHPs have lesser moral standing than humans but are still relatively high up—indeed just next to humans—then what treatment of them is justified? If it is not possible to specify research that is impermissible for NHPs because of their moral proximity to humans—precisely because their biological proximity requires their use instead of humans—then of what use is even the highest moral standing next to humans if it is not the full moral status of humans? Problems of this kind make many philosophers

⁵⁶ E.g. in moving from nociception, to pain sensations, to consciousness, to complex social interactions and expectations, to self-awareness, to rationality or some such scale.

concerned about the very idea that there could be different levels of moral status. Since we want to say that a *moral* obligation is a very serious sort of obligation, not to be overridden even by legal, and certainly not by merely pragmatic, considerations, it is hard to see how there could be levels of moral status other than “full”.

The second possible strategy for supporting a difference in moral status between humans and NHPs significant enough to justify the Animal Rule is to deny the assumptions of moral individualism. This denial could take two forms: the denial of the attribution of moral status on the basis of *individual* rather than group characteristics, or the denial of the tie between moral status and certain intrinsic properties (in particular, psychological capacities).

Some commentators have explicitly claimed that, despite overlap in individual capacities, we are justified in treating non-human animals in ways that it is morally impermissible to treat humans, because the proper yardstick is not the individual, but the group. For example, in a widely reprinted defense of the use of animals in biomedical research Carl Cohen writes, “Persons who are unable, because of some disability, to perform the full moral functions natural to human beings are certainly not for that reason ejected from the moral community. The issue is one of kind. Humans are of such a kind that they may be the subject of experiments only with their voluntary consent” (Cohen, 1986, p. 866). The problem, however, is that it is difficult to tell what the *argument* is supposed to be for this type of claim. Cohen simply asserts, but does not provide any particular reason for thinking, that humans as a group ought to be treated one way and animals another. In fact, Peter Singer responds to a different author’s similar defense of the group-membership based distinction in moral status between human and non-human

animals by writing, “I find it hard to see anything in this argument except a defense of preferring the interests of members of our own species because they are members of our own species.” (Singer, 1989, p. 85) We know of no particularly successful response to Singer’s critique of this strategy.

The second, more promising argument for a distinction in moral standing between humans and NHPs challenges the idea that moral status is determined by the *intrinsic properties* of individuals. Philosophically, this argument is appealing for two reasons. First, supporters of the intrinsic properties view are often unclear about what the specific connection is supposed to be between these properties and moral status. (Nor is it obvious exactly which properties should influence moral status.) Although it seems clear that a variety of properties, like the capacity to reason or to have complex psychological reactions, are important in determining what kinds of interests a being will have, it is unclear what the connection is to the level of moral attention we owe those interests. Moreover, the intrinsic properties view of moral status seems like a bad fit for explaining the level of moral consideration we think that we owe each other, let alone what we owe non-human animals.⁵⁷

So what are the alternative ways that we might think about moral status? One way is through relationships, rather than intrinsic properties. That is, we might think that the level of moral consideration we owe one another is an extension of the various kinds of relationships we have with one another.⁵⁸ For such a view to make sense as an ascription

⁵⁷ To give just one example, on the intrinsic properties view, the otherwise unremarkable (at least in modern societies) idea that human babies have full moral status is a problem that must be accounted for. The issue is not that the intrinsic properties theorists deny full status to babies—they usually find ways (through potential or other routes) to grant babies full moral status. The issue is that the intrinsic properties view seems to have gotten something fundamentally wrong if the moral status of babies is a problem at all.

⁵⁸ Warren (2000) discusses this kind of view in some detail (pp. 122-147)

of direct moral status, we must be clear that the relationship itself can be a source for direct valuing of the individuals within the relationship. If this is spelled out with some care, we think that the conclusion that relationships can be a source of only indirect moral status can be avoided. However, this view is still deeply problematic as a view about moral status, since it is not clear how it could support the claim that all persons have equal moral status. Surely, whatever we want to say about moral status, we do not want to claim that those persons who are loved or cared for have higher moral status simply because of their specific relationships with loved ones. Rejection of this conclusion thus returns us to what was appealing about the intrinsic properties view of moral status: namely, the possibility of attributing equal moral status to all beings with certain general properties.

How can we disentangle, then, the appeal on the one hand of equal moral status for all beings with certain intrinsic properties and the worry, on the other hand, that in particular those human beings without those properties will be considered to have lesser moral status? One possibility is to embrace plural sources of moral status: intrinsic properties and relationships, for example. Yet such a move still seems marginalizing for those humans without the relevant properties, since now their moral status seems dependent on forming particular kinds of bonds with others.

We would like to suggest instead that an underlying problem in the dominant strain of philosophical discussions of moral status is the assumption that there is a straightforward connection between ascriptions of moral status and prescriptions of obligations.⁵⁹ While some kinds of obligations seem to follow fairly straightforwardly from some specific types of moral status (for example, the obligation to respect certain

⁵⁹ This point and the specific ideas that follow come from Elizabeth Anderson (2004).

basic rights seems to follow fairly straightforwardly from the designation of a being as one with certain basic rights), much less can be said about what general types of obligation follow from which general considerations of relative moral status. In determining specific obligations, matters of social and personal context are critical.

In regard to this point, it is important to highlight an issue for laboratory animal care-taking that will receive more attention in section 2.C (on ABSL 3 and 4 laboratories). Researchers and other animal care-takers clearly have relationships with animals in laboratories that they do not have with animals in the wild. With these relationships come moral responsibilities of caretaking that are familiar to all. The essential question, then, is whether these relationships of care-taking are compatible with some of the uses that are at issue in BD/EID research. Or, alternatively, does the very relationship of caretaker-dependent ground obligations toward the animals at issue that are in conflict with some kinds of uses?⁶⁰ We are in no position to answer this question here, but simply raise it as highly significant in the context of this discussion of moral status.

We have now considered in detail the first strategy outlined by the Nuffield report in application to the issue of moral status of NHPs. We conclude that it is difficult at best to argue that all NHPs that are the subjects of BD/EID research aiming at product approval through the Animal Rule have lesser moral status than all potential human subjects. At the same time, we think the move from considerations of moral status to

⁶⁰ It is important that whether or not one is obligated in certain ways by a morally significant relationship is largely an objective matter – in other words the obligations that attend to the relationship of care-taker-dependent hold independently of whether a care-taker, for example, sees herself as either occupying that role or being obligated in these particular ways. If this were not the case it would be all too easy to avoid moral obligations by engaging in social or psychological “moral distancing”. C.J. Cuomo and L. Gruen discuss the phenomenon of moral distance toward non-human animals and others, which they understand as “accidental or intentional lack of spatial or emotional proximity that prevents us from adequately knowing or caring about whole categories of beings who are affected by our lives, actions, and decisions” (1998, p. 130).

obligations toward the beings at issue has often been too quick, and that specific contextual questions of social practices and individual relationships must be taken into account in order to develop a more complete picture of human obligations to NHPs in these contexts. We discuss these issues in more detail in section 2.Civ (on virtue ethics and ABSL 3 and 4 laboratory environments) below.

The second strategy that the Nuffield report outlines for arguing that the use of animals in research is permissible where human participation would be impermissible is to maintain that animal interests are so different from human interests that humans and animals are not adversely affected in similar ways by being treated similarly. Clearly, this claim must be made specific to a given context, as its truth or falsity is highly dependent on the species of animal and the type of use. Here we shall just mention a few specific issues that seem relevant to consider in the context of BD/EID research on NHPs.

First, it is likely that at least some NHPs have a level of self-awareness that makes killing them a type of harm that is quite different from “merely” cutting short the life of an animal with little or no sense of itself as an individual continuing over time. Furthermore, because of the strong social bonds and emotional capacities of some NHPs, the death of a group member can have serious social ramifications. These factors raise questions about the moral permissibility of killing NHPs that are different from the questions raised by the killing of some other animal species in research.⁶¹ In addition, many NHPs have the capacity not simply for pain but for suffering, which is a more complex phenomenon involving not merely unpleasant physical sensations but also complex psychological and emotional responses. Similarly, arguably at least, pleasure for

⁶¹ Yet, other than the 1997 NRCC conclusion that chimpanzees should not be killed for population control purposes (noted above, p. 59), we are aware of no special considerations that are required to justify killing NHPs post experimental use.

NHPs is not simply psychological “welfare”, which is well enough recognized in the regulations, but flourishing as a being of a particular kind. Thus, issues of how and whether suffering can be avoided and flourishing promoted in the research setting are significant (as we discuss in C.iii below). Finally, NHPs possess not merely the capacity for strong community ties that should be fostered, but also, in some species, the capacity for forming bonds with human care-takers. These bonds raise issues of special obligation, based on reciprocal emotional and cognitive understandings, that may legitimately place a human being under greater obligations toward particular animals. These are discussed in C.iv below.

Section C) ABSL 3 and 4 Laboratories and Animal Care and Welfare

i) High containment laboratories and BD/EID animal research

Because of the dangerous nature of the pathogens studied in BD/EID research, this research must usually take place in high containment laboratories. The recently updated US Government publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) (US Department of Health and Human Services (HHS), 2007) details the criteria used to differentiate laboratory containment levels 1-4. Important considerations for determining which containment level is required are “infectivity, severity of disease, transmissibility, and the nature of the work being conducted [and, where the agent causes at least moderate disease] the origin of the agent, whether indigenous or exotic.”(p. 17)

The designation of risk groups for infectious microorganisms from levels 1-4 is an international practice. For example, according to the WHO, level 1 risk is for microorganisms “unlikely to cause human or animal disease,” while level 4 is for a

pathogen “that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.” (World Health Organization, 2004, p. 1)

As the BMBL manual notes, however, the risk associated with research is associated with laboratory procedure hazards as well as agent hazards (US Department of HHS, 2007, p. 21). This is important for animal welfare because interaction with animals itself is a significant part of the risk involved in the research (US Department of HHS, 2007, p. 72).

In this section, we address a few features of high containment animal laboratories (animal biosafety levels (ABSL) 3 and 4) that raise particular concerns for animal welfare, including: certain physical features of high biocontainment laboratories and animal habitats therein, difficulties for human handling of infected animal subjects, and the special restrictions on personnel working in these laboratories. As we shall see, these concerns also relate to three key components for the operation of high containment laboratories: facility requirements (or secondary containment), safety equipment (or primary containment), and safety and security practices.⁶²

While it is important to highlight these practical concerns regarding the specific features of high containment animal laboratories that may impact on animal welfare, it is also crucial to consider the background ethical issues of human-animal relationships and animal flourishing that we think ought to inform how these concerns are addressed.

While the practical issues that have been raised about animal welfare in high containment

⁶² The BMBL notes “safe practices, equipment, and facility safeguards” as the three key components to protection of laboratory workers and communities (US Department of HHS, 2007, p. 31). They distinguish biosecurity, which is directed to “the protection of microbial agents from loss, theft, diversion or intentional misuse” from biosafety, which is concerned to “reduce or eliminate exposure of individuals and the environment to potentially hazardous biological agents.” (*ibid*, pp. 118-119) The BMBL further notes that these two aims can sometimes conflict, but in general are complementary (*ibid*, p. 119), and in any case, biosecurity is now an essential feature of laboratories in light of the 2001 anthrax attacks and 2003 Select Agent Regulations (*ibid*, p. 118).

laboratory settings are specific to those settings, the considerations of human-animal relationships and animal flourishing, although especially salient in the BD/EID research context, are general moral considerations that should be addressed with respect to animal research in any specific setting. We first outline the specific animal welfare issues for high containment animal research mentioned above and then suggest a virtue ethical framework for considering the issues of human-animal relationship and flourishing that underlie an adequate moral approach to these concerns.

ii) *Animal welfare concerns for high containment laboratories*

There is very little literature available dealing explicitly with ethical concerns about the care and welfare of animals within animal biosafety level (ABSL) 3 and 4 laboratories specifically, and no literature, to our knowledge, that positions these concerns with respect to a broader moral framework. The *ILAR Guide* (ILAR, 1996) offers detailed relevant considerations for general animal care and welfare for any laboratory that maintains an assurance with OLAW and/or receives AALAC accreditation. In addition, IACUCs are responsible for oversight of animal welfare, care, and use in these facilities regardless of containment level. Extensive literature is available regarding species-specific maintenance of animal welfare within research generally, and some limited training resources are available regarding animal care specific to high containment laboratories.⁶³ For ABSL 3 and 4 Laboratories, there are also a number of

⁶³ In response to a perceived severe shortage of veterinarians qualified to work in laboratory settings and, in particular, in high containment laboratories, the CDC recently announced a veterinarian training program for laboratory certification including “hands-on” training in ABSL 3 and 4 facilities (US Center for Disease Control, 2008 Aug 29). The American Biological Safety Association has issued a publication titled, “Anthology of Biosafety X: Animal biosafety (Richmond, 2007). Many of the resources discussed in Pritt et. al. (2007) are also relevant for animal care training specific to ABSL 3 and 4 laboratories.

resources available for biosafety training and information.⁶⁴ From our review of the relevant literature, we can identify at least three specific areas of potential concern regarding the care and welfare of animals in high containment facilities: 1) challenges of animal habitat in the facilities (related to secondary containment or facility features), 2) problems for human handling of animals (related to both primary containment features and safety practices), and 3) issues of training for animal care technicians, veterinarians, and/or researchers (related to safety and security practices).

Challenges of habitat for animals in high containment laboratories are necessarily specific to the species and the individual laboratory to some degree. However, some general features of these ABSL 3 and 4 environments, in particular some facility design (or secondary containment) components that ensure separation of animal facilities from human exposure, including directionality of ventilation and exhaust, lighting, and cleaning and decontamination of cages (US Department of HHS, 2007, pp. 97-98), could pose problems for animal welfare. For example, the repeat disinfection or sterilization of habitats could limit the types of cages and enrichment items that are practically feasible, and some of these limitations could affect animal well-being (Copps, 2005). As another example, since animal waste must be contained and treated, bedding for large animals poses a practical problem; however, “The total elimination of bedding poses an ethical problem” (Copps, 2005, p. 37). In terms of the more general facility environment, the overall stark quality of these laboratories, as well as specific noise, lighting and airflow

⁶⁴ See the summary of relevant guidance in Pritt, Hankenson, Wanger, & Tate (2007, p. 33), of particular significance are the BMBL (US Department of HHS, 2007) and Occupational Health and Safety in the Care and Use of Animals (Committee on Occupational Safety and Health in Research Animal Facilities et al., 1997) and Occupational Health and Safety in the Care and Use of Nonhuman Primates (Committee on Occupational Health and Safety in the Care and Use of Nonhuman Primates, & National Research Council, 2003).

qualities that are tied to safety and containment features, need to be assessed for whether they negatively affect animal wellbeing.⁶⁵

A second area of concern has to do with human handling of animals and maintaining safety for humans, on the one hand, and the welfare of animals on the other. Because animal contact is a primary suspected route for possible laboratory-associated infection (US Department of HHS, 2007, p.23) limiting human-animal contact also limits potential for bites, scratches, or other routes of infection. In high ABSL laboratories, human-animal contact is limited by controlling which individuals are allowed to enter the animal facilities and in terms of the type and frequency of contact (US Department of HHS, 2007, pp. 89-90, 92; Copp, 2005, p. 35). This area of concern relates to safety practices in high containment animal laboratories as well as primary containment devices, such as personal protective clothing for humans and physical containment devices for animals.

Some other safety practices that are important for human welfare may negatively affect animal welfare. For example, for reasons of human safety it may seem necessary to limit the numbers of animals within an enclosure, but group housing is important to the welfare of many species (Copp, 2005, p. 37).⁶⁶ To give another example, limiting human-animal interaction presumably would make the development of some alternative animal management techniques -- such as voluntary submission to blood draws -- difficult, since developing these techniques requires more extensive human-animal

⁶⁵ The Canadian Council on Animal Care *Guide to the Care and Use of Experimental Animals* has an especially accessible overview of environmental factors that influence animal welfare (Olfert et al., 1993).

⁶⁶ According to a 2003 survey of facilities in the US managing nonhuman primates while 73% of all primates lived in social housing, only 46% of those housed in cages or small indoor enclosures (i.e. those most likely taking part in biomedical experimental protocols) were socially housed (Baker, 2007).

interactions.⁶⁷

In high containment laboratories, handling animals only in physical animal containment devices or biosafety cabinets is part of the standard safety protocol (BMBL, p. 93). Contact is limited in part through the physical barriers created by protective personal equipment, which creates some problems for animal welfare. For example, with small animals, gloves that provide adequate protection can make it “difficult to gauge the pressure required to grasp the animal safely” (Copps, 2005, p. 38). Moreover, when the use of impervious personal protective barriers is insufficient to guarantee safety, other types of physical and chemical restraint are promoted. The BMBL specifically states a need to consider special practices in ABSL 3 laboratories, such as “the use of restraint devices and practices that reduce the risk of exposure during animal manipulations (e.g., physical restraint devices, chemical restraint medications, etc)” (US Department of HHS, 2007, p. 92). One author states that in practice, NHPs must be handled with chemical restraint (Copps, 2005, p. 38).

Finally, important concerns have arisen regarding the adequacy of training of animal technicians, veterinarians, and researchers in relevant animal care practices and welfare issues specific to high containment facilities. Reasons for a possible training gap include: the application of heightened security concerns to laboratory personnel, including select agent regulations; a lack of adequate knowledge base and training materials for use of animals in high containment facilities; and a limited number of qualified professionals who can oversee training. These concerns relate to both

⁶⁷ An interesting discussion of the possible ways in which NHP welfare could be improved by focusing on developing animal management techniques based on relationships of trust takes place in Kerwin (2005). Kerwin worked in NHP research laboratories between 1999 and 2004 and subsequently wrote an “open letter” report expressing her concerns that entrenched laboratory habits and restricted schedules undermine the potential to creatively improve NHP welfare in the laboratory.

biosecurity and biosafety practices. We have already briefly touched on the limited availability of qualified professionals and the paucity of training resources. It is important, however, to elaborate a bit on the apparent tension between biosafety and biosecurity with respect to training.

US select agent regulations require that laboratories both limit access to select agents and require security risk assessments for any individuals with such access (US Department of HHS, 2007, p. 384). These regulations create practical problems for training in appropriate animal care and management in high containment laboratories. Although “advanced biosafety is usually taught within a mentor-apprentice relationship” and “working safely with pathogens requires sound judgment, informed mostly by technical training and experience,” (Gronvall, Fitzgerald et al., 2007, p. 79) the requirement for security risk clearance “inhibits the practical exchange of safety-related information and techniques between high-containment laboratory researchers, by preventing, for example, a technician in one laboratory from demonstrating techniques in another laboratory without going through a separate lengthy process.” (Gronvall, Fitzgerald et al., 2007, p. 80).⁶⁸

iii) *Virtue of Care and Animal Flourishing Issues*

In this section, we propose that the animal handling and training issues discussed above are fundamentally about how to develop proper practical virtues of care within

⁶⁸ Jean Patterson, Chair of the Department of Virology and Immunology, Southwest Foundation for Biomedical Research expresses similar concerns in a 2007 interview. She says, “I worry about training. That’s from personal experience...neither CDC nor Ft. Detrick could let us in to have our vets trained” and “our attorney will not allow non-employees to work in the Level 4. Therefore, we can’t train anybody in Level 4” (Jean L. Patterson interview, from Drexler, 2007, p. 100)

ABSL 3 and 4 environments, in light of (1) difficulties with providing appropriate mentorship and (2) the safety and containment features of these environments, which of necessity both limit and distance animal-human interactions. We also propose that animal “welfare” concerns, including habitat issues, in these environments are best understood as difficulties with promoting species-specific flourishing. We think this focus on the need for appropriate habits of good care, mentorship, and norms of flourishing for the type of animal at issue is implicit—and sometimes explicit—in the approach that is taken to animal care and use in the literature on laboratory animal welfare; however, no general ethical framework is used to organize these concepts. Finally, we propose that a virtue ethical perspective could make some headway, both in providing a more comprehensive ethical framework for thinking about animal care and welfare and in providing some normative guidance.

iv) Why is virtue ethics a good fit for laboratory animal care?

It may not be immediately obvious why virtue ethics is a helpful approach in the animal research context. In this section we elaborate on why we think that an overarching ethical framework is needed for animal care and welfare issues in ABSL 3 and 4 laboratories and why we think a virtue ethical framework provides a good fit. Importantly, we think that our points here can be generalized to other animal research contexts and so are not specific to high containment laboratories, although the particular challenges that a virtue ethical framework will highlight—mentorship, building proper habits of care, and attention to animal flourishing—may be especially salient in these settings.

Earlier we discussed challenges to the 3Rs regarding animal use justification. Here we address issues of care and use of animals internal to the research context.⁶⁹ In this context, we think the 3Rs, while helpful, are also in need of supplementation with a more comprehensive moral framework. To see why, we need only consider for a moment the content of the 3Rs. Replacement is concerned with the use of animals, as opposed to human or non-living objects of research. Reduction is concerned with numbers of animals needed (or justified) for use in a particular research protocol, or with reduction more generally in the numbers of animals used in a particular type of research. Both replacement and reduction kick in, in other words, before the specific protocol even starts. That leaves us with refinement as the rule of thumb bearing all the moral weight *within* the laboratory setting itself. Some issues of refinement may be resolved before the start of a specific protocol—for example, choice of study endpoints (degree of morbidity, etc.), types of animals used, methods of analgesia or reduction of stressors. However, other issues of refinement that are clearly relevant within a research activity—for example, choices about whether to train capable animals to voluntarily submit to sample collections and forgo standard restraint mechanisms—might not always be properly identified as refinement questions.

Of course, the ethical issues relevant to the day-to-day practices of animal care and use in research are much broader and more varied than can necessarily be addressed by the notion of refinement alone. Encouraging appropriate human-animal bonding, reliability and consistency in care-taking practices, integrity in the collection of samples from animal subjects, placing animal welfare above personal time-tables and ensuring

⁶⁹ As we have already discussed, issues of justification and care and welfare necessarily overlap; however, even if we assume that the use of animals in the research context is justified, the specific moral issues of animal care and welfare in the context of research must still be addressed.

accommodation of study timetables to animal subjects' needs, and consideration of laboratory practice changes that might improve animal welfare offer just a few examples. Many of these specific practices are addressed by regulatory and professional guidance, including the *Guide*, standard operating procedures, and specific guidance for particular types of animals or research contexts. However, in the absence of a more comprehensive moral framework, the ethical significance of the discourse and practices around animal care and welfare is insufficiently appreciated.⁷⁰ An adequate explanation and justification for prescriptive moral claims about what should be done, pursued, valued, and supported in the context of animal care and use within the laboratory is simply missing. In short, what is needed is a framework both to adequately describe the nature of the moral issues arising in this context and to appropriately prescribe proper approaches to these issues within the setting.

Assuming, then, the need for a more comprehensive ethical framework, why is virtue ethics such a good fit? We have already discussed two aspects of this fit in part 1.Dii, where we introduced virtue ethics as a philosophical frame for considering the ethics internal to animal research. There we touched on the importance of habituation and mentorship in virtue ethics, particularly in laboratory animal research, and identified virtues as both nuanced and familiar dispositions to appropriate action, feeling, and attitude in specific contexts. Here we focus on a third and final area of fit between laboratory animal research and virtue ethics, and then turn to a specific consideration of

⁷⁰ This limitation shows up in interesting ways. For example, the kinds of issues that get flagged as “ethics” issues in the literature on animal care and welfare appear to be considered as such simply because they challenge some specific regulatory or practice standard—not for any reason related to ethics in a more comprehensive sense.

the issue of human-animal bonds in laboratories, in order to give a more detailed practical picture of how virtue ethics and animal research come together.

The third suggestion of fit between virtue ethics and laboratory animal research is specific to animal care and use, and involves the organizing concept of *flourishing* in virtue ethics.⁷¹ In predominant ancient and modern forms of virtue ethics, living in accordance with human excellence (or living virtuously) is intimately tied to human flourishing, which is our necessary aim as human beings.⁷² Flourishing has to do with species- or type-specific well-being, which is not necessarily undercut by mere pain sensations nor fulfilled by merely living a physically comfortable or psychologically stress-free life. Any individual animal (human or non-human) flourishes when it lives a life that is good for it, both as a particular kind and as a specific individual, where notions of “good for” are taken in part from a view of what is natural for it, and are assessed over its lifetime. For human beings, flourishing has to do with the exercise of moral and intellectual virtues; these particular modes of flourishing are not relevant for non-human animals.⁷³ Rather, the concept of flourishing for non-human animals simply captures an important type of well-being—one that is more comprehensive than the notions of psychological and physical welfare alone.

To give an example of when animal welfare and flourishing views diverge, we might consider polar bears living in a North Carolina zoo. Polar bears might live

⁷¹ In Greek, the relevant term is *eudaimonia*, which has been sometimes translated as “happiness”, “well-being”, or “flourishing”. None of these fit the meaning of *eudaimonia* quite perfectly, but the notion of flourishing is appropriate to our purpose here.

⁷² According to Aristotle, virtue is necessary but not quite sufficient for *eudaimonia*, which also requires some external support; on stoic views, virtue is necessary and sufficient for *eudaimonia*.

⁷³ There are complex questions for virtue ethics regarding whether this fact about non-human animals makes it impossible for them to partake of *eudaimonia*. Rebecca Walker (2007) argues in detail for the application of some aspects of this concept to non-human animals, with a particular focus on the interpretation of flourishing.

relatively comfortable and stress-free lives in the zoo, a habitat and climate radically different from what is natural for them in the circumpolar Arctic. Yet this assessment of the polar bears' *welfare* is not sufficient to determine whether polar bears can *flourish* in NC zoos, although it is certainly relevant, since physical and psychological welfare are necessary, but not sufficient, components of flourishing. Indeed, moral objections to keeping polar bears (at least those bears that might otherwise live well in their native habitats) in such zoos are not unreasonable, because part of the consideration of flourishing is a normative notion of the unsuitability of this habitat for this kind of animal. A similar discussion is currently underway about the suitability of the zoo environment for elephants. A recent report demonstrating that elephants suffer from obesity and behavioral problems in captivity has been challenged by those arguing that the risks posed to elephants in the wild are equally significant. (Dean, 2008)

When we think about animal welfare from a virtue ethics perspective, then, the promotion of animal flourishing is the organizing practical concept.⁷⁴ Thus, a crucial question is whether animals of particular types can live lives that are good ones for their kind within specific laboratory environments. Questions like this seem easy to answer for species of mice, for example, that are bred specifically for laboratory research. However, in the context of ABSL 3 and 4 laboratories, the overall starkness of the facility and the variety of necessary safety, sanitation, and/or security features (or the alteration of environmental features for reasons of safety and security), for both animal habitats and the general environment, may give rise to some difficult questions of fit for certain

⁷⁴ There is a move here from the importance of flourishing in virtue ethics as an individual human end to the promotion of flourishing for animals. This move is not much more difficult than the move between flourishing as an individual human aim to flourishing as an aim with respect to our treatment of other humans. For an in-depth discussion of why, according to a virtue ethics view, we ought to treat animals in ways that accord with their flourishing, see Walker (2007).

species of animals. Treating these questions of fit as issues of animal flourishing helps to broaden the discussion beyond focus solely on physical and psychological comfort (though both are essential to flourishing) to include pursuit of social and individual activities and type of habitat natural for the kind of animal.⁷⁵

We have discussed, then, three general areas of fit between virtue ethics and laboratory animal research: the relative familiarity and naturalness of character framing for moral issues and the multi-tracking of appropriate responsiveness that this framing entails; the contextual specificity of judgments regarding good attitude, action, and emotion and the concomitant need for appropriate mentorship and habituation; and the organizing concept of flourishing in considerations of animal welfare or well-being. To exemplify the interplay of these three areas of fit as applied to a single important issue within laboratory animal research, we think it is useful to sketch a virtue ethical approach to human-animal bonding or relationship.

Following Russow (2002, p. 34), we take human-animal bonds (hereafter HA bonds) to be, minimally, reciprocal relationships formed between humans and individual animals that tend to (though do not necessarily) promote increased well-being for both parties. The ethical issues related to HA bonds are of special interest for a virtue ethics approach to laboratory animal research generally, but have a particular import for high containment facilities. For philosophical approaches to moral theory that emphasize both

⁷⁵ We think it is important to note that concerns about animal welfare as commonly put forward in animal research do focus in great detail on species-specific habitat, social, and individual activity needs. This makes perfect sense in so far as concerns for animal physical and psychological welfare are tightly tied to maintaining standards that fit what is natural for the kind of animal. Still, there remain some important differences between welfare and flourishing. First, focus on flourishing as an organizing concept fits within the overall virtue ethics framework that we suggest is useful in animal research care and use in general. Second, flourishing as a normative notion offers an explanation of why, on the one hand, an environment that does not cause greater animal physical or psychological harm might still be problematic and, on the other, why mere pain or some psychological distress, if it occurs as part of an overall flourishing animal life, is not necessarily problematic.

the impartial treatment of moral equals and the principle-based determination of right action (as do both utilitarian and rights-based approaches), the moral elements of HA bonds may seem difficult to characterize or assess.⁷⁶ Treatment flowing from such bonds may appear, in these frameworks, to be problematic “moral partiality;” special obligations incurred within the relationship may be oddly characterized as “contractual” or as justified only given overall welfare considerations; and reactions of grief at the loss of the animal with which the human had formed a bond may appear as a non-moral side issue. In contrast, we think that the virtue ethical focal points we have been discussing—character, context, and flourishing—better account for the moral complexities of HA bonds within laboratory animal research.⁷⁷

In considering a virtue ethical approach to HA bonds, it is essential to identify which virtues are especially salient to these bonds. In this paper, we can do little more than list virtues that seem particularly appropriate, including: patience, respect, care, friendship, compassion, justice and reliability. A discussion of these virtues would indicate in more detail the scope of the human excellence in each, and its contrary vices of deficiency and excess, and would consider the particular ways in which these virtues would play out, with respect to HA bonds in general and specifically for these bonds in a animal research laboratory setting.

Of this list of virtues, the one that plays the most prominent role in Aristotle’s discussion of relationship is friendship. However, friendship to Aristotle is only

⁷⁶ For an in depth discussion of how the ethical issues regarding HA bonds in laboratory animal science are commonly presented in philosophical and psychological literature see Russow (2002) and Herzog (2002), respectively.

⁷⁷ Russow (2002) and Herzog (2002) each appeal to a care theory framework as more appropriate to HA bond assessment. We agree with this point, since care theory and virtue ethical perspectives have much in common (for a discussion of this point see Noddings, 2007). Yet, for the specific reasons we outline in this paper, we think that a virtue ethical perspective is particularly promising.

applicable to inter-human relationships of a very special nature, as it requires living together and sharing in virtuous pursuits (Aristotle, 1985, books VIII, IX). It is an open, and interesting, question whether a virtue of friendship between human and non-human animals can be made sense of.⁷⁸ The other virtue listed that merits comment is justice. Justice is not clearly a virtue of special relationships or bonds; in fact, there is a distinct lack of a need for justice in the impersonal sense in the context of friendship.⁷⁹ However, in the context of laboratory animal research, at the very least distributive justice is an applicable virtue, because humans need to be careful that their bonds with particular animals do not undermine the well-being of the other animals for which they are responsible. This might happen, for example, if one animal in a group is always singled out for individual attention, thus reducing the time that the researcher or technician has to tend to the needs of the other animals.

Because virtues require appropriate action, feeling, and attitude, all oriented in context to the proper subjects, times, and manners of interaction, it is clear that cultivating the virtues appropriate to HA bonds will involve a number of different exercises of practical wisdom. Just a few of many possible considerations are mentioned here. For example, one will not want to try to form bonds with animals incapable of reciprocity. In contrast, there is a *prima facie* reason for a human who bears some responsibility for a particular animal's well-being to try to form a bond with the animal

⁷⁸ C.J. Cuomo and L. Gruen suggest that we can be friends with some animals as long as we understand friendship in an "expanded" sense that focuses on the "heartfelt connection" we have to some animals (1997, pp. 136-137). Further, they argue that forming these bonds can help us to expand our moral orientation and avoid the moral distancing that underlies some human oppression of nonhuman animals (pp. 131-138).

⁷⁹ The complex relationship between some aspects of justice and friendship goes all the way back to Aristotle who notes, for example, "if people are friends, they have no need of justice, but if they are just they need friendship in addition; and the justice that is most just seems to belong to friendship" (1985, 1154a25).

when forming a bond is possible and could promote the animal's well-being. If the aim of the bond is mere convenience for the care-taker, however (for example, less time spent cleaning cages because the animals are more willing to follow the care-taker's direction), then forming a reciprocal *bond* seems inappropriate, since such bonds carry moral obligations, such as care and fidelity. However, especially when animals are social and are in need of interaction not otherwise provided, HA bonds might be particularly important to cultivate. Finally, far from being an oddity or non-moral side issue, emotional responses of grief or sadness at the loss of the animal with which one has formed a bond are appropriate and, indeed, called for on a virtue ethical approach.

The exercise of practical wisdom to determine appropriate action, feeling, and attitude with respect to HA bonds, as exemplified above, illustrates just one aspect of the contextual determination of virtue. Here we merely mention two other features of the contextual determination of virtue, which highlight the differences between a virtue ethical framework and a moral framework based on principle-based reasoning. First, in virtue ethics, morality is not primarily an application of impartial principles or rules of action to specific contexts. On the one hand, action does not necessarily take priority in moral significance (although it is, of course, very important); on the other, no general "hard and fast" principles of action are appropriate, since proper action is context-dependent and moral "rules" hold only for the most part (Aristotle, 1985, 1094b20). Second, because in a virtue ethical framework moral action is not a function of the application of impartial principles, "partial" treatment of individuals on the basis of HA bonds (or personal relationships generally) is not a deviance that must be justified, but is as much the norm as impartiality. The proper adjudication between "partial" and

“impartial” treatment of individuals is a matter of the contextual applications of the appropriate virtues (friendship and justice, for example).

HA bonds are important for a discussion of flourishing with regard to both parties to the bond. On the one hand, the issue of HA bonds helps to clarify some of the complexity of the notion of animal flourishing and “naturalness for a kind”. If we focus too much on what is natural for a kind to the detriment of considerations of what is good for the individual, then we might draw the conclusion that HA bonds should not be formed with non-domesticated animals. But in contrast to this possible conclusion, three points should be noted. First, flourishing is not a notion that calls for a simple appeal to “the natural” as normative where what is natural is somehow purely biologically determined; rather, the very notion of “natural” is imbedded with norms in this context.⁸⁰ Second, a determination of flourishing appeals to what is good for an animal both as an individual and as a member of a kind.⁸¹ These considerations can, of course, diverge. Finally, and most important, practical conclusions with regard to promoting animal flourishing are, as always, context-sensitive. Although a HA bond *might* undermine the well-being or flourishing of a highly social primate in the wild, in a laboratory setting such a bond might present a significant opportunity for the same type of animal to express its social nature.

For the human party to a HA bond, considerations of flourishing primarily have to do with the exercise of the virtues themselves. On a virtue ethical view, as already

⁸⁰ Rosalind Hursthouse’s chapter on naturalism is most helpful in spelling out a virtue ethical naturalism that neither relies on a purely scientific-objective account of human nature nor relies on a foundational appeal to moral naturalism (1999, pp. 192-216).

⁸¹ For complex social animals, Hursthouse identifies individual survival, species continuance, characteristic freedom from pain and enjoyment, and social functioning as all relevant to a naturalistic evaluation of flourishing (1999, p. 202).

discussed, to be an excellent human being is precisely to have and exercise the moral and intellectual virtues. This does not mean that such factors as psychological and physical well-being do not contribute to flourishing. As is the case with non-human animals, these factors are important; in addition, for humans they are integral to the exercise of the virtues themselves. Thus, in the context of laboratory animal care, the value of HA bonds will depend on whether they encourage the appropriate practice of important human virtues relevant to the context of animal care. If, as is not implausible, human psychology is such that the development of proper virtues of care, reliability, and compassion all require the exercise of deeper connections to individual animals, such as take place in HA bonds, then HA bonds will be essential both for human and for animal flourishing in the research context.

This last point brings us to a core concern regarding human and animal flourishing in the context of high containment animal laboratories. Given the safety principle of limiting human-animal contact as much as possible, and given the distancing that human protective barriers creates between humans and animal subjects in the laboratory, HA bonds could be highly limited in these contexts, if possible at all. If, however, these bonds are important for animal well-being, on the one hand, and the development of the proper virtues of care-taking on the other, then this limitation is highly morally significant.

A focus on virtue ethics in laboratory animal research highlights the importance of virtues of character as multi-track dispositions to act, feel, and perceive in ways appropriate to time, place, and subject. Moral assessments and practical determinations in all these areas are specific and context-sensitive, and are founded on continued exercise

in habituation to virtue and appropriate mentorship. The organizing concept of flourishing is appropriate, in different ways, both for considering the well-being of animal subjects and for the development of virtue in human actors (researchers, technicians, veterinarians). In the context of virtue ethics, then, the animal welfare, handling, and technician/researcher/veterinarian training issues that arise in high containment laboratories are best understood as concerns about animal flourishing and the development of virtues that are important for animal care. We focused at some length on the question of HA bonds and the relationship between these bonds and the development of the virtues of care; however, we could as well have detailed the approach more thoroughly with respect to mentorship, or to environmental features affecting animal flourishing.

v) Virtue ethics and ABSL 3 and 4 laboratory Q&A

In closing this section of the paper, we present a list of specific practical questions that we think deserve more attention in the context of ABSL 3 and 4 laboratory environments. We offer a few brush-stroke considerations regarding each question.

1) Which virtues are especially relevant to laboratory animal science, and of these, which are of particular relevance in the context of high containment work?

We think it likely that the relevant virtues are the same; the relevant difference between lower and higher containment levels may be an issue of the difficulty of cultivating the virtue in that setting. Of special importance for all kinds of animal research are: compassion, scientific integrity, reliability, practical wisdom, friendship, patience, respect, care, and justice. Some of these virtues are more relevant to animal

care, some to interactions between humans. Each virtue should be given much more focused attention than we have been able to offer here.

2) *What is the most effective means of character building and mentorship, and how can these be undertaken in high containment laboratories?*

Here we simply note a point that has so far gone without discussion. A core tenet of ancient forms of virtue ethics is that virtuous traits of character in general require proper habituation and upbringing from a very early age (though no full form of virtue is possible before the achievement of practical wisdom, usually at an age well beyond young adulthood). In so far as this is true (and we might find this claim somewhat less convincing in light of modern emphasis on individual self-determination), the habituation that we are discussing in the practical virtues of a specific profession must be built on a scaffold of a fundamentally strong character. That is, these professional virtues are just specific practical turns on more general moral virtues, and cannot be cultivated, in the professional context, “from the ground up”.

3) *Virtue ethics seems to give a lot of good advice with respect to the care and use of animals within the laboratory environment, but would a virtue ethical approach to animal research ever conclude that a particular type of experiment or use of animals is morally unacceptable?*

Indeed, any use of animals that is inconsistent with virtue on the part of the researcher and/or care-taker would be morally impermissible. For example, we think it very hard to conclude that experiments on severe social deprivation in primates are consistent with compassionate treatment of these animals.⁸² Since a context-based

⁸² Of particular significance are Harry Harlow’s highly controversial experiments on maternal deprivation and mother surrogates in infant macaque’s in the 1950’s mentioned above in footnote 54 (Harlow, 1958),

determination is necessary for an adequate determination of the moral permissibility of any research project, what seems of special importance is to take very seriously the idea that some kinds of experiments may not be acceptable and that considerations of compassion, respect, integrity and the other virtues mentioned above may be decisive in these considerations.

4) Supposing a virtue ethics perspective can offer some insight on issues of justification, why do we still need to consider issues of moral status?

We think focus on a particular case both highlights the contribution that a virtue ethics approach makes to ethics internal to animal research practices and, at the same time, shows the importance of relative moral status considerations.

One example of the application of elements of practical wisdom to animal care in BD/EID research is found in NHP studies of the molecular genetics of variola, conducted under the Animal Rule by the CDC at USAMRIID's ABSL 4 facility (Jahrling et al., 2004). Because smallpox had not been seen before in NHPs, determining how best to assess and treat pain, discomfort, and distress in animal subjects required a degree of understanding of smallpox in humans, the ability to analogize to the experience of NHPs, the sensitivity and foresight to plan in advance to address potential distress, and the compassion and creativity to devise appropriate measures under the circumstances. USAMRIID investigators sought consultation with experts about how best to care for NHP subjects in this research; together, investigators and consultants devised creative

but especially his later experiments on total social isolation of NHPs in the 1960's. See, for example, Harlow et al. (1965). It is interesting that those who have written about Harlow's experiments have also been especially interested in his character and in either what effects the studies had on him or what it was about him that moved him to conduct these experiments. See for example, Slater (2004, pp. 133-157). Slater writes, "Why did Harlow want to see such things [of Harlow's Iron Maiden or "evil mother" surrogates]? Animal rights activists say he's a sadist, pure and simple. I, myself, don't think that's it, although what drove him- the variables- I cannot quite detect." (2004, p. 142).

means of addressing animal subjects' pain and distress, for example, easing mouth sores by means of frozen fruit pieces instead of lidocaine mouthwash, and treating lesions on animals' hands, as especially important for NHPs' ability to function. (Neill, 2005)

In this case we think it clear that researchers and their consultants exercised certain key components of practical wisdom in devising appropriate assessment and treatment of the pain, discomfort, and distress in the animal subjects of this research. Nonetheless, the question whether this type of research (smallpox research on NHPs) is justified at all is a matter for serious debate, as we have discussed in much detail. Concerns about justification of this type of research seem to stem primarily from the apparent extreme discounting of NHP interests relative to human interests and a worry about whether benefit to humans will in fact result from this research. The key moral concern does not seem to focus on an assessment of the researchers' character and behavior toward the animal subjects. Further, there is a significant practical issue of how a virtue ethical approach would be able to determine whether the research in this specific case was justified. The clear virtue ethical position would be that whether this research is justified depends, at least in part, on whether a fully practically wise researcher would engage in it. However, it is difficult to determine the implications of this position. If we were to conclude that this research was unjustified, it would nonetheless probably be difficult to argue that the treatment of NHPs in this research was necessarily cruel from a virtue ethics perspective, while at the same time recognizing that the researchers' approach to the animals' experiences and needs under the circumstances included important virtues like compassion and concern. Thus, a virtue ethics approach, while

important and useful, is not alone sufficient when addressing the full scope of ethical considerations in this context.

We hope that, through this and other examples, we have at least begun to demonstrate the contextual complexity of the relationship between considerations of moral status, research justifiability, and the ethics internal to the practice of animal research, and to suggest the value, but also potential limitations, of a virtue ethical approach in helping to address these considerations in practice.

Part 3: Implications for Policy and Practice

It is by now, we trust, very clear that the care and use of animals in potentially harmful research conducted solely for human benefit presents ongoing challenges that extend well beyond BD/EID research. It is just as clear, however, that the rapid expansion and at least some of the particular attributes of BD/EID research invite closer scrutiny of the care and use of animals, and in addition highlight some of the persistent moral tensions and challenges in animal research. We hope that the discussion we have offered of these issues will serve as a backdrop for further exploration and assessment on the part of animal researchers, policy makers, and interested humanities researchers and scholars.

In this final section of the paper we seek principally to suggest several practical and theoretical tools to assist BD/EID researchers in their goal of using animals in a morally responsible manner where such use is justified. To that end, we briefly discuss three recommendations regarding the Animal Rule and ABSL 3 and 4 laboratory animal care and use training:

(1) Additional clarity is needed on the use of the Animal Rule and the role of animal models. Investigators and scholars called upon the FDA to clarify and refine their guidance on the use of the Animal Rule, and in response, the FDA has issued new draft guidance (US FDA, 2009c). Ideally, such guidance ought to improve 2 of the 3 Rs—that is, reduction and refinement—even if replacement is not possible. Whether the draft guidance is sufficient to the need remains to be seen.

(2) Training needs for ABSL 3 and 4 labs should include animal care and use as a priority. A persistent irony of BD/EID research is the tendency for increased security to be incompatible with increasing safety. In screening and training personnel for high-level containment laboratories, security concerns can override safety concerns, with detrimental effects not only on the very availability of appropriately qualified personnel, but also on the thoroughness of safety training. Similarly, as we have seen, both security and safety can impair animal welfare in precisely the same ways—by reducing the availability of qualified personnel, impoverishing the environment of laboratory animals, and diminishing relative attention to education about animal welfare—which, in the ABSL 3&4 environment, must necessarily be more intensive to be meaningful.

(3) Virtue ethics should be considered as a potentially fruitful theoretical approach to practical ethics education in ABSL 3 and 4 laboratory animal care and use. Even after the development of more detailed guidance for use of the Animal Rule, it is clear that specific instances of BD/EID research will continue to present ethical challenges in balancing animal flourishing with data-gathering and containment priorities. In addition, animal researchers do, and should continue to, address whether particular uses of animals are morally justified. Laboratory workers (whether technicians

or investigators) who cultivate bonds with animals as an integral component of their research are likely to find it congenial to think of the details of their obligations to these animals as flowing in part from their relationships with them, but even when such relationships are not possible, key virtues such as integrity, compassion, and fidelity to promises will be salient and meaningful to consider in the context of animal care. Identified relevant virtues can be employed to explore the most appropriate features of study design and conduct in particular instances of ABSL 3 and 4 research. In addition, at least *part* of an adequate analysis of whether or not a particular use of animals is morally acceptable should stem from a consideration of the compatibility of that use with these same and other relevant virtues (such as justice).

While it is beyond our purview here to detail more precisely how a virtue ethical model might be employed in BD/EID research with animals, we believe that virtue ethics' intuitive appeal, capacity to express context-sensitive moral nuance, and appeal to adequate mentorship and practice hold promise. At the very least, virtue ethics is a helpful addition, both to the 3Rs and to other moral frames for effectively grounding the goals of good study design and conduct, security, and animal flourishing that characterize this research. Moreover, we believe that the practical advice and personal and community expressions of the moral considerations salient for experienced animal researchers and technicians could readily be elicited in qualitative research and shared in peer education as a key component of a virtue ethical approach. BD/EID research presents great technological and ethical challenges; yet there is a great need for research results that can benefit humans. For these reasons it seems incontrovertible that researchers and policymakers should continue to make every effort to uphold and

improve animal and human flourishing for those involved in this research and, at the same time, to take seriously the need to address the broader justificatory issues in a publicly accessible manner.

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Appendix

Regulations, Policy, and Guidance for BD/EID Animal Research

Kind	Name	Entity of Oversight/ Implementation	Significance for BD/EID research
US Law	Animal Welfare Act of 1966	APHIS of USDA	Authorizes regulation of the transport, sale, and handling of dogs, cats, nonhuman primates, guinea pigs, hamsters, and rabbits intended to be used in research or "for other purposes."
	Animal Welfare Act Amendments of 1970	APHIS of USDA	Expands coverage to all warm-blooded animals determined by the Secretary of Agriculture as being used or intended for use in experimentation or exhibition, with an exception for farm animals used in food research. However, not enforced with respect to mice and rats bred for research and birds.
	Health Research Extension Act of 1985 (Nov 20), Section 495: Animals in Research	OLAW of NIH	Mandates PHS policy on Animal Care and Use Committees.
	Food Security Act of 1985 (Dec 23), Subtitle F - Animal Welfare	APHIS of USDA	Establishes regulations for exercise for dogs, psychological well-being for non-human primates. Specifies that pain and distress must be minimized in experiments and that alternatives be considered. Institutional Animal Care and Use Committees are introduced.
	Project BioShield Act of 2004	NIH and NIAID	Authorizes \$5.6 billion in funding over 10 years for development and purchase of priority medical countermeasures, and grants expedited and simplified award of grants and contracts for the development of critical medical countermeasures.

Kind	Name	Entity of Oversight/ Implementation	Significance for BD/EID research
US Policy	PHS Policy on the Humane Care and Use of Laboratory Animals	OLAW of NIH	Applies to “live vertebrate animals” used in PHS supported research.
	PHS Principles for the Utilization and Care of Animals Used in Testing, Research and Training (1986)	OLAW of NIH	Reflects US interpretation of the 3Rs.
	Memorandum of Understanding (2006)	Between the USDA, FDA, and NIH	Sets forth a framework for inter-agency reciprocal cooperation in promoting proper laboratory animal care and welfare, intended to enhance effectiveness while avoiding duplication of efforts.
	Animal Efficacy Rule (2002)	FDA	Provides for approval of certain new drug and biological products based on animal data when adequate efficacy studies in humans cannot be ethically conducted.
	Select Agents Regulations	CDC and APHIS of USDA	CDC regulates possession, use and transfer of biological agents that pose a severe potential threat to public health and safety. APHIS regulates those that pose a potential threat to animal and plant health or to the safety of animal or plant products.
	NIAID Priority Pathogens	NIAID of NIH	Lists pathogens in order of research priority for NIAID Bioinformatics Resource Centers.
US Guidance	Animal Biosafety Levels 1-4 (2007)	Published jointly by the CDC and NIH.	Provide increasing levels of protection to personnel and to the environment, recommended as minimal standards for activities involving infected laboratory animals.
	PHS Guide for the Care and Use of Laboratory Animals (1996)	Published by ILAR, National Research Council.	Offers detailed relevant considerations for general animal care and welfare for any laboratory that maintains an assurance with OLAW and/or receives AALAC accreditation.
Intl Guidance	3Rs Framework for the Reduction, Refinement, and Replacement of animals used in biomedical research	No official US regulating entity.	Today widely embraced by animal research communities and international arenas governing animal research. The US policy interpretation is reflected in the PHS Principles.
	Association for Assessment and Accreditation of Laboratory Care	AAALAC, an international, private, nonprofit	Promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. Perceived as a de facto requirement in the US to attract staff, researchers, and funding.
	CIOMS International Guiding Principles for Biomedical Research Involving Animals (1985)	CIOMS, an international, non-governmental, non-profit	Intended to provide useful criteria to which academic, governmental and industrial bodies may refer in framing their own codes of practice or legislation regarding the use of laboratory animals for scientific purposes.

