From Unpleasant to Unbearable - Why And How to Implement an Upper Limit to Pain And Other Forms of Suffering in Research with Animals.

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Abstract

The focus of this paper is the requirement that the use of live animals in experiments and in vivo assays should never be allowed if those uses involve severe suffering. This requirement was first implemented in Danish legislation, was later adopted by the European Union, and has had limited uptake in North America. Animal suffering can arise from exposure to a wide range of different external and internal events that threaten biological or social functions, while the severity of suffering may be influenced by the animals' perceptions of their own situation and the degree of control they are able to exert. Severe suffering is more than an incremental increase in negative state(s) but involves a qualitative shift whereby the normal mechanisms to contain or keep negative states at arm's length no longer function. The result of severe suffering will be a loss of the ability of cope. The idea of putting a cap on severe suffering may be justified from multiple ethical perspectives. In most, if not all, cases it is possible to avoid imposing severe suffering on animals during experiments without giving up the potential benefits of finding new ways to cure, prevent, or alleviate serious human diseases and generate other important knowledge. From this it follows that there is a strong ethical case to favour a regulatory ban on animal experiments involving severe suffering.

Key words: animal experiments; animal suffering; ethics; humane endpoints; refinement; severe suffering

Introduction

There are two main discussions about the use of animals in potentially harmful biomedical and other forms of research. The first is about *whether* to use animals, the other is about *how* to use them.

The first, most fundamental discussion questions the moral acceptability of using animals for experiments for the sake of human benefit where these experiments cause harm in the form of discomfort, pain, or other suffering and are nearly always followed by killing the involved animals. This debate about whether at all to use animals in research and testing is dominated by thinkers who, based on a variety of ethical positions such as utilitarianism, animal rights, or virtue theory, favour a view to the effect that it is always wrong to use animals for such experiments.[1]

The second discussion takes a more conventional, anthropocentric starting point which does not question the premise that it is morally acceptable to use animals for research and testing aimed at important goals such as finding new ways to cure, prevent, or alleviate serious human diseases. Rather, this debate is about which requirements must be fulfilled for such animal-based research to be morally acceptable. So far, two kinds of requirements have been discussed. One is that scientists should strive to minimize harm to animals involved in research and testing, exemplified by a focus on the so-called 3Rs, i.e., on ways to Reduce the number of animals used to the minimum necessary for scientific validity, to Replace experiments with live animals with alternative methods, and to Refine procedures of the remaining animal experiments so as to avoid or minimize animal suffering.[2] The other is that animals should be used only when that use is likely to give rise to genuine benefits to humans (or animals), or to ensure that there is a proper

68 balance between harm imposed to animals and expected benefits. It is fair to say that the 3Rs
69 today have been implemented as an integral part of the way animal experiments are regulated
70 and reviewed across at least the Western World, and that the requirement for some sort of a
71 Harm-Benefit Assessment preceding animal experimentation also has a wide uptake,[3] although
72 not universally embraced.[4]
73
74 This paper addresses a third requirement relating to animal experimentation, which is to put an
75 absolute cap on the suffering that animals may endure as part of an experiment. According to this
76 requirement experiments should *never* be allowed if they involve *severe suffering*. Of course,
77 this requirement could be seen as a special case of the requirement to Refine procedures, but
78 whereas the requirement to refine is always relative to what is possible without sacrificing the
79 goal of the research, this requirement is absolute.
80
81 Such a requirement has been in place in Danish legislation for more than two decades and is
82 included in the recent European Union directive which defines the minimum standards of the
83 regulation of animal experimentation put in place in each of the 28 EU countries. Thus in the
84 directive (Article 15(2)) it is said that "Member States shall ensure that a procedure is not
85 performed if it involves severe pain, suffering or distress that is likely to be long-lasting and
86 cannot be ameliorated"[5]; however, there is an important modification in the form of a safeguard
87 clause to which we will return.
88
89 Such a ban of animal experiments involving severe suffering seems to cut across the ethical
90 discussions mentioned above. On the one hand, it is presented as another requirement within a

context where the moral legitimacy of using animals for experiments is not questioned and it therefore seems to belong to the second of the above presented discussions, the one focusing on *which type of experiments* are morally acceptable under a general assumption that at least some are. On the other hand it seems to ban certain experiments out of a concern for protecting animals without considering the potential benefits of the experiments foregone and may therefore be seen as being in line with the view that it is always wrong to use animals in harmful experiments found as one side of the first discussion. Part of the aim of this paper is to discuss whether, and to what extent, a ban of experiments involving severe suffering could be situated within the more conventional and anthropocentric debate on animal experimentation.

The main claim in this paper is that there are strong moral and scientific reasons in favour of a ban on animal experiments giving rise to severe suffering. These reasons are that severe suffering involves a qualitative step-change in negative state which we summarise as from unpleasant to unbearable *and* that it seems possible, to a large if not full extent, to avoid severe suffering without jeopardizing research progress. Even if there were cases which posed a real dilemma between the concern to avoid severe suffering and allowing research of potential vital human benefit we argue that there can be good moral reasons to uphold a ban.

Our starting point will be to trace the origin of this idea and explore the degree to which it has been implemented in legislation and guidance documents in different parts of the world. After that we will consider what is meant by suffering and outline its different forms. Following that we will discuss how severe suffering differs from other unpleasant experiences, arguing that severe suffering is not just more of the same but involves a qualitative leap from unpleasant to

unbearable. In light of that we discuss two main ways of underpinning a ban on severe suffering in terms of ethical theory which will align with either an abolitionist or a more conventional line of thinking. We will then discuss how in practice to draw the line between non-severe and severe animal suffering. Furthermore, we discuss to what extent it is possible to implement a ban on severe animal suffering without forgoing important benefits such as finding new ways to cure, prevent, or alleviate serious human diseases. This discussion ends with a guardedly optimistic view. Finally, before concluding we discuss from the view of the main ethical positions outlined how best to deal with the possible cases where there is a real dilemma between avoiding severe animal benefits and potential vital benefits to human health.

Origin of the Idea of an Upper Limit to Suffering and Its Implementation in Different Parts of the World

The idea of banning suffering beyond a certain level is first found, to our knowledge, in a report issued by the Danish Animal Ethics Council – an advisory board set up according to the Danish law on animal protection. In a statement from 1992 the Council argued that an acceptable ethical stance regarding the use of animals for experimentation and testing requires that one considers the perspective of all affected parties and that "when aiming to take the perspective of the affected animals, one cannot help to view strong pain and other severe suffering as ethically problematic"[6] (the senior author of the current paper, PS, was then chairman of the Council and drafted the report). The report recommended that experiments involving strong pain and other forms of severe suffering should be prohibited according to Danish law. A revision of the Danish law with this ban implemented was passed by the Danish parliament in 1993.[7] According to § 7

of that law an animal may not as part of an experiment "experience strong pain, other intense suffering or intense anxiety".

Examples of applications which have been rejected in Denmark in light of the ban include toxicological studies with death as an endpoint (personal communication Axel Kornerup Hansen, University of Copenhagen) and neurobehavioural experiments involving inducing learned helplessness (personal communication Leif R. Lund, the Danish Animal Experiments Inspectorate). There do not seem to be many other examples. However, it is likely that in light of the legislation, many more possible applications have not been submitted or have been withdrawn or modified in the light of informal communication with the staff of the Animal Experiments Inspectorate.

The idea was later taken up by the European Union and implemented in the most recent Directive 2010/63/EU,[5] defining minimum requirements to be implemented in national legislation in all EU countries. In the Directive, Article 15(2) requires that "a procedure is not performed if it involves severe pain, suffering or distress that is likely to be long-lasting and cannot be ameliorated".

However, in the EU rules, unlike the Danish case, the ban on such procedures is not unconditional but linked to so-called "safeguard clauses", to the effect that the requirement can be suspended "for exceptional and scientifically justifiable reasons" (Article 55(3)). If taking such a measure, an EU Member State is obliged to inform the European Commission within a month. By July 2019, no such notifications had been received by the Commission (Susanna

Louhimies, personal communication). Whereas this may be considered reason for cautious optimism that indeed, no experiments are done in which animals are made to suffer severely, it is also important to notice that whether a procedure is considered to involve severe pain, suffering, or distress and what is understood as long-lasting are the responsibilities of review committees to define in each individual case. As guidance is relatively general, without specific examples of what makes suffering count as severe and/or long-lasting, and there are several hundred review bodies in the EU,[8] there is likely to be considerable variation in how these rules are applied.

The idea of an upper ceiling for suffering of animals used in research also exists in regulatory documents outside the EU. The strongest position is found in Canada, where the guidance for protocol review states that "Procedures that involve sustained and/or inescapable severe pain or deprivation in conscious animals (…) are considered highly questionable or unacceptable, irrespective of the significance of anticipated results."[9]; however, such experiments can still be approved and in 2017 involved 2% of all animals used in Canada.[10]

There is also no upper limit on laboratory animal suffering allowed under US laws and regulations. However, when conducting experiments classified as Category E (unalleviated pain and/or distress, included in mandatory annual reports of animal use submitted to the federal government by registered research institutions[11]), researchers need to provide additional justification that there is no acceptable alternative to the protocol as proposed. In practice, there is considerable variation between how Institutional Animal Care and Use Committees in the US review outcomes in general[12] general and specifically as to what is judged to be alleviated versus unalleviated pain or distress (Category D versus E), what constitutes temporary (Category C)

versus longer pain or distress (Categories D, E), and what is an acceptable alternative (see also[13, pp173-183]). It should also be noted that the definition of Category E is based on whether or not pain or distress is alleviated rather than on how severe the pain or distress is.

Other nations and regions of the world appear similarly to avoid imposing limitations on experiments inducing severe and prolonged pain or distress.[14]

So the idea of an upper limit to the suffering that an animal may endure during an experiment has already been implemented, at least partially, in some parts of the world. However, to make full sense of that, more needs to be said about what animal suffering is. To this we will now turn.

What Is Suffering And Which Forms of Suffering Exist?

In the animal welfare literature, the term suffering has been used both as a generic term for negative subjective experiences, and to identify negative experiences that are especially severe or prolonged[15,16] . On the latter view suffering is therefore viewed as more than an unpleasant but routine part of life. Having to give a talk to a large audience may induce anxiety, while strenuous exercise is likely to result in muscle pain. Yet some of us even volunteer to give a plenary lecture or run a marathon. And few would argue that transient, self-induced, and relatively mild unpleasantness equals suffering. These experiences are not intense or long-lasting enough to affect our mood or to interfere with our capacity to carry on our daily life. The situation is not very different from the more common ailments that affect modern humans. A head cold may interfere with our capacity to concentrate, to enjoy food and even to sleep well, but it lasts only a

few days. A stomach bug or the flu may indeed make one feel desperately ill but, again, the unpleasantness is usually short-lasting and we assume we can endure it without lasting trauma.

So even though "suffering" as a technical term may sometimes be used to cover all forms of negative subjective experiences there is an everyday use of the term where such experiences counts as suffering only when they are intense or long lasting. Many humans consider they are "suffering" only when one intense or long lasting negative experience (e.g. pain or disease) is further accompanied by other situational factors (e.g. extreme fear, loss of control or lack of social support) to the point that their condition seems unbearable and their sense of self is threatened[16 citing Cassel 1982]. In light of this usage the phrase "mild suffering" which is found in EU regulation of animal experimentation[5] may seem to be an oxymoron. Similarly, our use of the term "severe" might be considered unnecessary. However, precisely because phrases such as "mild" or "moderate suffering" are used in a diverse scientific and regulatory literature, we retain use of the term "severe suffering" whilst acknowledging that many of the examples we discuss will mirror states defined by some[16] simply as "suffering".

Pain has traditionally been seen as the primary or the most likely contributory component of suffering. However, during the 20th century there was a growing awareness that other forms of subjective experience could also contribute to suffering. The following definition of suffering was provided by the 1965 British Report of the Departmental Committee on Experiments on Animals (The so-called Littlewood Report) and subsequently adopted by the Brambell Committee's report[17] (note that the adjectives negative and positive here are used to refer to whether the sign is absent (negative) or present (positive), not to whether or not it is desirable):

(a) discomfort (such as may be characterised by such negative signs as poor condition, torpor, diminished appetite); (b) stress (i.e. a condition of tension or anxiety predictable or readily explicable from environmental causes whether distinct from or including physical causes); (c) pain (recognisable by more positive signs such as struggling, screaming or squealing, convulsions, severe palpitation).

These different kinds of states may be distinguished by their sensory origin. Thus pain originates in the detection of threat to bodily integrity or function. Many other threats are similarly detected by animals' sensory systems, including thirst, hunger, cold, heat, nausea, dizziness, and breathlessness.[18] In animals with a capacity for conscious experience, the detection of each of these threats may be accompanied by negative subjective experiences. However, there are also forms of suffering that reflect animals' perceptions of their external situation without being linked to specific forms of sensation, e.g., fear and anxiety. Finally, there may be negative mental conditions which are not tied to the perception of external events, such as depression.

The study of animal emotion focuses on understanding the multi-component (behavioural, cognitive, and subjective) responses of animals to these situations. Russell[19] developed an influential and useful framework to consider emotion. His core affect model characterizes emotions on two dimensions: valence (positive/negative) and arousal (energy/lethargy). Human emotions situated within this dimensional space include anxiety, fear, panic, frustration, anger, helplessness, loneliness, and boredom.

Whereas there is some debate about whether using such names or labels to describe emotions in animals is valid, the core affect model can be applied to animals without naming specific emotions,[20] and indeed core affects exist in humans without being labeled, interpreted, or attributed to any cause.[19] Humans share basic emotional brain-behaviour circuits with other vertebrate species[21-23] and it is quite valid to consider, for example, fear and anxiety as emotions generated within the amygdala, which lead to freezing or fleeing responses in most vertebrate species. But many of the other emotional systems identified by Panksepp and others, particularly those associated with the evolution of social attachment (lust, care, nurturance), may be restricted to mammals and some birds.

From an evolutionary perspective, negative emotions are useful for animals in shaping behavior both in the short (act immediately to get away from a negative experience) and the longer term (learn to avoid something which in the past has resulted in negative experiences). The ability to act on negative experiences is equally important as regards a negative emotional experience such as fear. If the animal responds appropriately, then fear (however intense) may be fleeting and transitory.

But for laboratory animals, sometimes suffering can become severe because the experimental protocol or in vivo assay prevents the animal from taking any effective steps to remove the threat. So lack of control compounds the threat itself – animals in confinement cannot avoid imposed heat or go elsewhere to find food – and eventually if nothing is done to mitigate impact, animals may die in studies of extreme environmental challenges.[24,25]

Indeed, there is a body of work that demonstrates that animals that are able to control or terminate their exposure to negative events have significantly improved welfare relative to animals that experience exactly the same events (including duration and intensity) but for which the events are uncontrollable.[26,27] This may explain why an inability to control exposure to aversive events is strongly associated with the development of Post-Traumatic Stress Disorder (PTSD), a debilitating psychological condition in humans. In PTSD, fear is experienced frequently and repeatedly, outside of the initial fear-inducing event. A "typical" procedure to induce PTSD in an animal model is to immobilize rats in cones and place them in a cage next to a cat in a situation that they cannot escape.[28]

We can see that suffering can arise from exposure to a wide range of different external and internal events that threaten biological or social functions. The severity of suffering generated may be mediated by the animals' perceptions of their own situation and the degree of control they are able to exert.

What Makes Severe Suffering Qualitatively Different from Other Unpleasant Experiences?

The moral view that there should be an upper limit to how much animals should have to endure in research and testing may appear to involve simple quantitative reasoning: the more (in terms of duration and intensity) there is of this bad thing the worse it becomes and one has to draw the line somewhere. But it is also possible to argue that severe suffering is qualitatively different from other levels of suffering in a way that is morally relevant and which justifies an absolute limit.

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299 To make our case we will turn to the study of the human psychology of suffering and the
300 interaction between distressing experiences and wider aspects of human functioning. Thus, based
301 on an analogy with human suffering, we hope to make vivid a qualitative difference between
302 negative subjective states that fall within the adaptive coping capacity of the individual and
303 where recovery is possible, versus severe suffering where intense or long-lasting negative
304 experiences are accompanied by other situational factors, to an extent that profound and long-
305 lasting damage is caused, and a full recovery may not be possible.

306

307 One way that a human copes with negative subjective experiences that are not too severe and not
308 too long lasting is keeping them at arm's length by focusing on the more exciting or positive
309 aspects of one's life. In the short-term someone with flu may still listen to the radio or get
310 pleasure from hearing they have obtained a reward of some sort, while in the longer-term
311 someone who has lost a leg may focus on a new hobby such as painting. However, under some
312 circumstances there may simply be so much pain or other negative experience that there is little
313 room for anything else in one's attention and little possibility of distraction. If pain or other form
314 of suffering is long-lasting, it may become part of one's perception of who one is and what one's
315 life is. The Schema Enmeshment Model of Pain in human psychology describes a situation
316 where an individual in chronic pain is unable to separate their self from their pain.[29]

317

318 In psychology, schemas refer to cognitive frameworks which seem inherently difficult to apply
319 to non-verbal animals. Testing this in humans relies on verbal associations which are difficult to
320 transfer to animals. Taking a wider view, associations between cognitive ability and capacity to

suffer must be carefully evaluated and differing cognitive capacities of species should be distinguished. Some animals (e.g., corvids, some primates) use episodic memories, the capacity to remember where, when, and what happened in the past, as a template that allows them perform a degree of "future" thinking and planning.[28] In terms of suffering, however, such cognitive capacity may be a double-edged sword. A future-thinking animal may be able to anticipate both the termination of a short-term painful event and the onset of further pain. On the other hand, as has been argued by Rollin,[31] the lack of ability of most animals to anticipate the end of suffering may add panic or despair to an already unpleasant experience.

An important feature of severe suffering is that it dominates attention in a manner that is qualitatively different from other forms of negative experience.The dominance of suffering will prevent one from carrying out everyday behaviours. Asking persons to identify how much their pain interferes with normal life is in fact one of the approaches used in research into and clinical management of chronic pain.[32]

Situations of severe pain, stress or social loss are important risk factors for depression in humans but many of the features characteristic of depression in humans (anhedonia, reduced activity, negative cognitive bias) are also present in animals that have been exposed to analogous situations. Whereas depression can be described as losing the capacity to enjoy life, in the most extreme situation, a huge emotional trauma may lead to the loss of will to live and in fact even be deadly, a situation sometimes referred to in clinical psychology as "give-up-itis". This is a "quantitative regression from normal, adaptive, goal-directed behaviour that passes through a

clinical spectrum from withdrawal, apathy, aboulia and psychic akinesia to psychogenic death.”.[33]

The concept of adaptive behavior is critical to our understanding of a qualitative difference between severe suffering and other forms of negative experience. In response to a wide range of challenges, a human or animal shows allostasis,[34] an adaptive response is mounted, and stability can be regained after physiological or psychologically stressful events have ended. Some degree of suffering may occur during an allostaic response but this will not have a long-lasting or dominating effect on the animal’s life. Events that result in severe suffering, on the other hand are destabilising and physiological or psychological stability cannot be regained even if the external situation improves. Severe suffering is thus associated with a failure to cope (such that a current trajectory will lead to premature death) or with a long-term struggle to cope whereby all resources have to be devoted to counter the situation. In such cases the individual is fundamentally changed for the worse.

In humans, extreme anxiety and depression can result in life-threatening sequelae such as ischemic heart disease or catatonia[35]. Animals too can clearly die from depression and other forms of severe suffering if they fail to cope. Harlow[36] reported an experiment where four infant monkeys were raised with warm cloth-covered surrogate “mothers”. Repeated or prolonged chilling of the surrogates produced increasing frequencies of severely disturbed behavior and by the end of two weeks, Harlow concluded that the procedure had precipitated the death of one of the infants.

366 Affected animals may give up eating or maintaining other vital tasks, but it is impossible to
367 assess directly whether or not they would judge their own lives to be no longer worth living.
368 Whether life is worth living is not something that can be objectiely measured and deciding this
369 is, in humans, perhaps the ultimate subjective calculation. Tragically, some humans do judge that
370 their lives are not worth living and take steps to end them. Whatever the specific circumstances,
371 such people have found their situation unbearable, and understanding their perceived reasons
372 (whether right or wrong) is an important goal in understanding how to prevent others reaching
373 the same point.
374
375 Systematic analysis of notes left behind by people who have died by suicide[37] reveals the
376 startling influence of social factors. People who feel they are a burden to others, or that they do
377 not belong to a group, are at particular risk of judging life to be not worth living. Loneliness in
378 humans is also associated with other serious declines in physical and mental health.[38,39] The
379 importance of social factors shows that we should be aware of the impact of social loss, social
380 defeat, and social isolation as potential sources of severe suffering in those species capable of
381 forming close social attachments. The total social isolation of young monkeys, for example, with
382 the devastating long-term behavioural consequences that result,[40] can indeed be expected to have
383 produced animals whose lives were filled with severe suffering.
384
385 The examples presented here from the human clinical literature and the corollaries drawn to the
386 animal scientific literature make vivid the conclusion that severe suffering is more than merely a
387 quantitative increase in negative state. Weary[16] has argued that whilst there may be quantitatively
388 different levels of pain or disease, this only becomes “suffering” (or in our terminology “severe

suffering") when when the original negative experience becomes overwhelming, threatening an individual's very sense of self. The shift to unbearable may be precipitated when intense pain is accompanied by negative situational factors such as loss of control, fear or anxiety or lack of social support. We encourage others to consider how this shift might best be recognized in animals.

Our starting proposal (not necessarily exclusive or complete) is that severe suffering occurs when negative experiences dominate attention; there is limited capacity for distraction or compensation; normal life cannot be pursued; full recovery cannot occur even if the external situation improves; or (in humans) one's own life is judged not to be worth living. We develop this theme with some practical examples in the section How to Measure Severe Suffering.

How Should the Idea of an Absolute Cap on Animal Suffering Be Underpinned in Terms of Moral Theory?

The idea of putting an absolute cap on the level of suffering to which animals may be exposed seems to add an element into the moral framework underpinning the use of animals for experimentation that goes against the overall consequentialist idea of weighing harms of the animals used against the potential benefits of the research. According to this consequentialist idea there should be no limit to how severe suffering animals should be allowed to experience in research, provided that the potential and likely benefit of the research or testing is high enough and provided it is not possible to achieve the same benefit through an experiment or a test where the animals experience a lower level of suffering.

One way to understand the idea of an absolute cap is by saying that the ethical theory underpinning animal research should indeed include a deontological constraint not to expose animal in our care to severe suffering. This seems to be the position of Beauchamp and Morton.[41] They frame the position within their version of pluralist principlism, where the cap follows from the application of the principle of non-maleficience: "For research animals, as for humans, pain is pain, suffering is suffering, and distress is distress, wherever they occur—in animal laboratories no less than human healthcare centers. As levels of these harms increase, they could reach the level of brutal, inhumane, and merciless actions. The more investigations approach these levels, the more a policy of firm upper limits is needed."[41(p443)]

The view expressed by Beauchamp and Morton does seem to contain a element often associated with deontology, the idea that motives and not just consequences matter for the moral assessement of actions – what is problematic about conducting experiments where animals can be foreseen to endure severe suffering seems, according to the quoted view, not just to be what happens to the animals but that the animals are deliberately subjected to "brutal, inhumane, and merciless actions" perpetrated by humans.

It is also possible to envision a version of this view in line with a classical animal rights position where focus is solely on the rights of the recipient not to be exposed to non-trivial harms, including severe suffering, rather than on the motives of the agent.

However, even on utilitarian and other consequentialist views, focusing on achieving the best possible balance of welfare across animals and humans, it may be possible to justify an absolute cap on research involving severe suffering – not based on an argument to the effect that that imposing severe suffering is in principle wrong (be it grounded on requirements for certan motives or on appeal to absolute rights) but on more pragmatic considerations: if scientists are allowed to do experiments with severe suffering, many of them will find a justification for why their experiment qualifies; if scientists are not allowed to do experiments with severe suffering, they are likely to find an alternative way of achieving the same aim without imposing severe suffering on the animals. In addition, an experiment that intentionally results in severe suffering may be poor science because data obtained from such an animal may have little relevance to the purpose of the experiment. Given the high moral weight that a consequentialist should give to preventing severe suffering (cf previous section) these considerations certainly make sense.

So-called two-level consequentialism, originally developed by R.M. Hare[42] and later applied to animals by Gary Varner[43], may be evoked to underpin the just presented line of thinking: the idea here is that most people are bad at making consequentialist calculations. They will tend to underestimate the harms to animals when they are believed to be necessary to achieve human benefits or to acquire scientific scientific knowledge. Therefore in most cases it will, from a consequentialist view, be better to abide by simpler principles. One such simpler principle could be not to allow animal experiments where the animals are likely to endure severe suffering. Of course, an even more simple principle would be to ban all experiments involving any form of suffering. However, this principle may have too large negative effects on research to be acceptable from a consequentialist point of view.

Even on anthropocentric terms, according to which animal welfare does not matter in its own right, there may be reasons to try to put at cap on the suffering that animals are allowed to endure, based on the reality[44] that severe suffering will be unacceptable for many people in society that, in turn, can erode public support for animal research.

The conclusion here is that the idea of putting a cap on severe suffering may be justified from multiple ethical perspectives. Much will hinge on the extent to which there will be a real dilemma between the concern for avoiding severe suffering in animals and ensuring that research of importance to human and animal health is undertaken. In what follows we will explore to what extent it is possible to avoid imposing severe suffering on animals during experiments without giving up the potential benefits of new ways to cure, prevent or alleviate serious human diseases. Before we get to that we will say a bit about how to measure the level of suffering in animals and specifically how to draw the line between severe and less than severe suffering.

How to Measure Severe Suffering

Existing guidelines and assessment frameworks[45] typically refer to aspects such as frequency, intensity, and duration of aversive events as a way to determine severity of suffering. However, to apply this in a qualified manner also requires insight into how animals are affected by the total load of aversive experiences (including a consideration of additive, multiplicative, and cumulative effects[46-48]) to which they may or may not habituate.

Many techniques have been developed to measure the degree of animal suffering arising from mildly unpleasant experiences or from more severe events. For example, the suffering evoked by rough handling, electric shock, or a noxious chemical could be assessed by measuring an animal's active avoidance responses (e.g., the effort expended by fish to avoid chemicals in the water[49]). However, for many species, exposure to such events can provoke innate responses such as "freezing" in place or withdrawal that can interfere with appropriate active test responses.[50] In these situations, passive tests provide an alternative approach. These measure the extent to which an animal will either *refrain* from moving towards a particular stimulus[51,52] or forgo desired resources such as food or social contact[53] to avoid an aversive event. In yet other contexts where there is no clear external focus, conditioned place preference tests (CPP) can be used to assess the degree of suffering arising from states such as chronic pain or anxiety.

CPP tests are based on the observation that animals can develop associations between distinctive locations and their own internal state. For example, hens with keel fractures[54] and mice with bladder cancer[55] prefer locations where they were previously given analgesic drugs over control locations where no pain relief was available. Animals that are free from injury or disease exhibit lesser or no such preferences, showing that the CPP test does give us insight into suffering that would otherwise remain invisible.

However, all of the above methods are problematic when it comes to measuring severe suffering. Very high levels of pain or stress will interfere with an animal's ability to store and recall information.[56] At such a point, the ability of animal to take control and "tell" us anything about its own state becomes limited. In addition, none of the standard methods of assessing animal

503 welfare focus on the qualitatively distinct features of severe suffering outlined previously. The
504 importance of careful analogy with humans therefore becomes even more critical. We can
505 consider those situations that result in severe suffering in humans and explore whether (and
506 which) animals may share similar experiences. Some forms of human suffering (dread of a
507 meaningless future, or despair about the state of the planet) may require cognitive processing that
508 is beyond the capacity of any other animal species. But severe human suffering due to other
509 causes, such as chronic pain or loss of a close social companion, can produce analogous
510 responses in animals, even if these cannot be formally measured using the usual methods.
511
512 Instead, rather than focusing on simple welfare indicators (cortisol levels, bruises, etc.) or
513 measures of preference or aversion, the identification of severe suffering in animals may require
514 us to measure depression-like states of withdrawal and apathy,[57] hyperactivity, or other changes
515 which reflect profound changes in general (non-system-specific) arousal, activity, and brain
516 function.[51] In addition, we should consider those permanent and fundamental changes that occur
517 when allostasis can not longer be maintained. Korte and collaborators[34] mention changes such as
518 violence, chronic fatigue, or atrophy of brain regions as signs that an animal is no longer able to
519 mount an adaptive response. Such asssesments of severe suffering should also measure the extent
520 to which damage or injury in one functional system affects other functional systems, like the
521 extent to which severe pain may greatly reduce appetite, mobility, sleep, or disrupt social
522 behavior. As a specific example, researchers attempting to induce PTSD in animals deliberately
523 measure a range of outcomes to ensure their protocols have produced not only a specific negative
524 experience such as extreme fear (in response to repeated exposure to predatory stimuli) and/or
525 pain (in response to respeated electric shock) but a wider range of life-changing impacts that

might model human traumatic experience. Thus, researchers will ensure that their protocols also evoke other responses such as extremely reduced exploratory behavior, persistent hypervigilance, memory of fearful events and changes in blood pressure[28, 59].

Whereas it is of course important to be able to measure suffering, it also seems reasonable to assume – until proven otherwise – severe suffering in higher vertebrates and other similarly complex animals in situations that are known to cause severe suffering in humans, and where the suffering in humans does not depend on cognitive capacities that are beyond the capacity of the animal in question.

So to conclude, just as for humans, suffering in animals will be influenced by intensity, duration, and loss of control. The qualitative tipping point may be signified when suffering dominates their attention, compensation cannot occur, normal life cannot be experienced, and) the animal cannot fully recover and will be fundamentally changed even if the external situation improves.

Are There Ways to Avoid Imposing Severe Suffering Without Forgoing Animal Research of Importance to Finding New Ways to Cure, Prevent, or Alleviate Serious Human Disease?

To attain consensus on limiting the severity of endpoints in animal research protocols, it may help to ask why severe endpoints for animal models of disease and injury are employed in the first place? The historical answer involves using animals to model not only the pathogenesis of a human illness or injury, but its severity as well. Extensive suffering and eventual lethality in

549 animal models have been considered *de rigueur* if those outcomes occurred in the corresponding
550 human patient. This linkage remains entrenched in the biomedical research establishment even
551 though our understanding of disease advanced from organismic to microscopic and molecular
552 scales long ago for many severe medical conditions.
553
554 Reluctance to adopt less severe endpoints can be due to peer pressure to have one's research,
555 grant proposal, institutional animal protocol, submitted manuscript, or regulatory acceptability
556 comply with established norms, as heard over many years by two of us (IASO and SMN).
557 Arguments have been published to the contrary, that less severe endpoints for severe diseases are
558 not only more humane but may also offer better scientific precision than allowing an afflicted
559 animal to continue to deteriorate and ultimately become moribund or succumb.[13,60] But progress
560 in implementation of such endpoints has been glacially slow for animal models of many severe
561 diseases, such as sepsis,[61] cancer,[62] and amyotrophic lateral sclerosis,[63] to name a few.
562
563 From the above conflicting viewpoints, one realizes that a fundamental intellectual, and some
564 argue morally justified, basis for retaining severe endpoints in animals that model severe human
565 illness or injury comes from government agencies responsible for reviewing, approving, and
566 regulating new medical products for those indications. Regulators have usually insisted that, for
567 diseases and injuries that can be fatal, clinical trials of a new product must demonstrate a
568 statistically sound improvement in patient longevity before market approval can be given; in the
569 oncology field, this has evolved from "overall survival" to "progression-free survival".[64] Since
570 improving patients' lives via better drugs and medical devices is the goal of biomedical research,
571 it follows that getting those products to market is a major criterion for achieving that goal.

572 Regulators' requirement for extended patient longevity implies and even mandates to many
573 scientists that animal subjects administered a trial drug, etc. likewise must live (longer) while
574 untreated animals must die (sooner), thereby making severe animal suffering and eventual death
575 unavoidable.
576
577 However, if established clinical regulatory convictions are deemed a valid rationale for
578 reluctance to consider less severe animal model endpoints, then more recent clinical regulatory
579 perspectives offer hope. Most prominently starting with the AIDS crisis almost 40 years ago,
580 when patients with AIDS were dying by the thousands and hundreds of thousands of persons
581 infected with HIV were likely to die given the absence of effective treatments, the US FDA
582 replaced AIDS patient longevity with an alternative endpoint to accelerate approval of new anti-
583 retroviral drugs. It had been established that the number of CD4+ leucocytes circulating in the
584 blood in HIV+ persons was highly correlated with and inversely proportional to an individual's
585 likelihood to develop AIDS and die. A stronger and direct correlation quickly followed, between
586 the amount of HIV-RNA in the blood and AIDS progression to death. With those relationships
587 confirmed, FDA began approving drugs with no or tolerable side effects that slowed the decline
588 of one's CD4+ blood cell count and prevented HIV-RNA blood levels from rising, even before
589 patient survival data were collected and analyzed. This radical change in approval criteria
590 allowed many drugs to become available sooner and saved countless lives.[65]
591
592 The use of CD4+ cell counts and HIV-RNA blood levels are merely early examples of so-called
593 "surrogate endpoints" as alternatives to survival that have been adopted as approval criteria for
594 many human clinical trials.[66] Also known as biomarkers, such measurable changes in body

595 weight, a blood constituent, tissue biopsy, or radiological image can provide literally vital insight
596 into the efficacy and safety of new drugs in clinical trials well before death. Because surrogate
597 endpoints can be scientifically validated and get new drugs to market faster and at less cost, drug
598 approval agencies in developed countries are promoting these endpoints in a coordinated
599 fashion.[67]
600
601 The question then arises: if regulatory review of new medical products for a given severe or fatal
602 disease does not require worsening illness or death of patients as the ultimate benchmark of
603 scientific progress before approval can be granted, then why must animals modeling those same
604 diseases experience severe suffering or death? This question revolves around severe illness or
605 injury for which much of the physical or chemical elements of disease progression are well
606 known and, therefore, relatively easy to identify as potentially informative surrogate endpoints.
607
608 But what about severe mental illnesses that can be just as debilitating and create just as much
609 suffering, even in the absence of equivalent cognition, in the corresponding animal subject? No
610 comparable surrogate endpoints like those mentioned above have been adopted yet for conditions
611 such as severe depression and anxiety. That is probably because the underlying causes for these
612 and other diseases of the mind have not yet been elucidated to the same degree. Considering the
613 societal gains offered by clinical surrogate endpoints in general, there is an ethical as well as a
614 scientific imperative to investigate and validate changes in empirical markers of severe mental
615 illness prior to the patient or research animal reaching a dismal state. For example, loss of smell
616 is a common early feature of Alzheimer's Disease in both humans[68] and rodent models[69], and
617 behavioural changes can predict severe outcomes in mice modeling Huntington's Disease.[70]

Regardless of the existence or not of candidate or regulatory surrogate endpoints or clinical biomarkers, the severity of suffering in many animal models also can be mitigated by providing supportive care to those animals without jeopardizing the scientific aims of the protocol. In modeling illness and injury in animals, we too often omit non-specific components of medical care provided to patients, such as warmth, quiet, hydration, nutrition, and companionship that may have no bearing on a given drug's activity but would be unconscionable as well as illegal to withhold at bedside. Animal models can be similarly enhanced to reduce the severity of pain or distress with no or acceptable adjustments necessary to one's experimental objectives.[71]

To wit, if one is developing new treatments to restore cardiac muscle contractility for congestive heart failure (CHF), why not administer diuretics to the animal model to avoid or delay eventual hypoxia or drowning from fluid buildup in the animal's lungs (especially if one is not studying pulmonary congestion that accompanies a progressively weakening heart)? Provision of diuretics is standard supportive care in human and veterinary patients with CHF, and would similarly prolong the life of the laboratory animal subject to enable a longer period of observation and data generation. Not only is the animal more comfortable but the "model" would now encompass a more representative clincal scenario to judge those experimental treatments better.

It is encouraging to see that medical regulators have started to acknowledge the scientific as well as ethical merit in providing supportive care to animals modeled to severe and fatal illness. For example, the FDA's Guidance to Industry for product development under the so-called Animal Rule states for animal models, "Investigational drugs should be evaluated within the context that

reflects anticipated clinical use" and "When included in an animal efficacy study, supportive care ideally should reflect the intended conditions of use of the investigational drug. It also should reflect the intended types of medical intervention and the timing of the availability of medical intervention expected in the human clinical or incident setting.".[72] Even more heartening, the Implementation Working Group for ICH Guideline S9: Nonclinical Evaluation for Anticancer Pharmaceuticals is allowing supportive care such as antibiotics for animals on toxicology studies that have secondary infections from test article-induced immunosuppression because "Patients with cancer are often given supportive care (e.g., antibiotics)".[73]

What to Do in Cases Where It Is Not Possible to Avoid Imposing Severe Suffering Without Prohibiting Vital Research?

We have been arguing that there is a strong ethical case to ban animal experiments involving severe suffering. An easy way for us to avoid having to face difficult dilemmas would have been to claim that it is always possible to avoid imposing severe suffering on research animals without having to face any loss in terms of scientific and medical outcomes. However, this would have been an inappropriate avoidance of reality.

In fact. many will, argue that there are quite a few actual cases where there would be a real dilemma between preventionpreventing severe animal suffering and enabling research of potential vital human importance. Take a lethal, painful and highly contagious human disease such as that caused by the Ebola virus (EBV). This was firmly established as a lethal pathogen in humans for many years, with a case fatality rate upwards of 80% in actual outbreaks. To mirror

that outcome, macaque monkeys used in EBV research were given lethal doses of virus to see if a candidate vaccine or anti-viral drug of interest would prevent death[74], with no winners emerging from decades of trying.

But during the 2014-2016 outbreak in West Africa, the case fatality rate averaged 40%, often correlating extensive and prolonged supportive care with a better prognosis[75]. This, in turn, required researchers to modify their previous assumptions and revise (refine) their animal models to encompass a wider range of possible clinical outcomes. One hopes that that such refinements will identify candidate vaccines and anti-viral drugs of sufficient promise for clinical trials without relying solely on animal survival (following severe pain and distress) as the primary endpoint. In the context of the discussion above, there may be reason to believe that surrogate endpoints or biomarkers may be reliably informative of protection or efficacy in earlier or milder stages of infection before the inoculated animal subject becomes sick to a point where it must endure severe suffering.

What if one is studying severe pain or distress itself? Our contention remains that with new scientific discoveries amid an acceleration of understanding how molecules, cells, tissues, and organs behave and can be studied in health and disease, the study of severe pain or distress does not, *de facto*, require equivalent states in animal subjects. Instead, and like other areas of research on severe diseases and injuries, new combinations of experimental approaches are possible that are just as informative without involving severe animal pain or distress.

We invite others with a different opinion to offer specific examples of exceptions to a ban on severe pain in animal research where there will be a real dilemma between the concern to protect animals against severe suffering and the concern to find new ways to cure, prevent, or alleviateserious diseases in humans and animals. In the meantime, it would be dogmatic of us to deny that such examples could be forthcoming. Therefore, the question arises whether such experiments should be allowed and undertaken. In the rest of the section we will aim to address this, possibly hypothetical, question as well as a raft of other ethical questions: 1) Do the means always justify the end? If we accept that torture should not be allowed, even in situations where it could serve to save many lives, should we not take a similar stand here? 2) Do animals ultimately matter less than humans when it comes to vital human issues? 3) Does it matter what species the animal is, whether it is a chimpanzee, a mouse, or a fish? 4) Should the experiments still be allowed, even if you personally find o them unacceptable?

The answers to these questions will clearly depend on one's ethical outlook. To simplify, we will elaborate on responses from three kinds of outlooks presented above: an animal rights view, a deontological view giving room for some animal experimentation, and a consequentialist view.

On an animal rights view the answer is simple. Since on this view the means never justify the ends when it comes to imposing harm on an innocent third party, since sentient animals in principle matter equally to humans, since species is in principle morally irrelevant, and since the law should protect rights, such experiments should not be allowed and undertaken.

According to the kind of deontological view defended by Beauchamp and Morton and referred to above, the answers will be much less clear. Here the means can justify the end only if the end is important enough (not all deontologists are pacifists). Humans will ultimately matter more than animals (that is why animal experimentation is accepted in the first place). Species may matter since some animals are more human-like than others. There may be a distinction between what one will not accept personally and what should be banned by law. So this kind of view could end up accepting a very stringent safeguard clause that would allow for certain exceptions to a general ban on animal experiments involving severe suffering.

According to a consequentialist view the answer is clear *in principle*: the end always justifies the means if there is the right balance of harms and benefits. Animals and humans matter equally when interests are of the same sort. Species does not matter in its own right. And laws should be put to use to achieve the best possible outcomes. So, in principle an experiment that could save many human lives should be allowed and undertaken no matter whether it would also cause severe animal suffering. However, given the kind of two-level consequentialism described above things may be less clear *in practice*. This is so because allowing experiments under special circumstances that give rise to severe suffering may lead to a slippery slope where, as today, far too much suffering is imposed on animals compared to the expected human benefits.

An illuminating analogy may be made to the case of using torture on humans. A consequentialist should, in principle, be in favour of allowing torture in extreme cases where it may help to save the life of a large number of innocent people. However, an adherent of two-level consequentialism may have good reasons to support a total and fully enforced legal ban on

torture. This may be based on evidence that torture does not normally serve its purpose of making people reveal critical information and, secondly, the reasonable expectation that without such a ban a lot of unnecessary torture would happen. Thus in consequentialist terms a ban on torture may bring about better net consequences than allowing exceptions for the rare cases. However, the question remains to what extent the animal experimentation case is analogous to the human torture case. Would it in the animal experimentation case be possible to enforce a reasonable safeguard clause?

Unless one adheres to a consistent animal rights view, there is no simple black or white answer to the ethical question of whether or not to allow severe animal experiments in exceptional circumstances regulated by safeguard clauses. There will be room for differences in opinion, and the authors of this paper may have slightly different views on this issue. However, we fully agree that much more needs to be done than is currently done, to limit experiments where animals have to endure severe suffering.

Conclusion

We have argued that severe suffering is qualitatively different from less severe suffering. Severe suffering may be recognized by more than one sign, but we highlight certain tipping points where suffering dominates all aspects of an animal's life, where it cannot find any compensatory pleasure, where it struggles to maintain normal function and is fundamentally changed, where its fear turns into PTSD, its sadness to depression, and its recovery is unlikely. These criteria should be implemented in documents giving guidance on how to classify levels of animal suffering.

754 Crucially, we also argue that severe endpoints are typically no longer necessary in animal models
755 of severe disease, injury, and in vivo assays due to an enlightened clinical regulatory framework
756 that continues to evolve in a positive (i.e., more humane) direction and should influence future
757 preclinical study design. So the old notion that only severe endpoints are acceptable to peer
758 review for funding, publication, protocol approval, and eventual regulatory acceptability is no
759 longer defensible. Second, even if animals are "required" to decline in health (e.g., one is
760 studying the actual physiology of extreme endpoints or dying), those animals will not have to
761 suffer as badly if they are provided simple and common supportive care, which, of course, needs
762 to be applied in a thoughtful manner to minimize any resultant data "noise". In most cases, such
763 measures will be able to prevent suffering from becoming severe.
764
765 So, if we are right, severe endpoints no longer need be tolerated in the vast majority of
766 experiments or tests involving laboratory animals, and medical progress will not be impeded by
767 embracing those Refinements needed to avoid severe suffering. From this it follows that not only
768 from ethical positions whose aim is immediate abolition but also from more anthropocentric
769 ethical stances will it make sense to favour a regulatory ban on animal experiments involving
770 severe suffering.
771
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