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An ethical analysis of the 3Rs

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Abstract

Even though the 3Rs (i.e., Replacement, Reduction, Refinement) are widely accepted as ethical standards when evaluating research projects using animals as experimental subjects, the ethical status of the 3Rs still remains to be clarified. The 3Rs were not derived from any ethical theory, but they represented an attempt to increase humanity to animal experimentation and at the same time to improve validity of scientific data (Russell & Burch, 1959). The aim of the present article was to provide an ethical analysis of the 3Rs through Engelhardt's bioethics theory (1998). The analysis revealed the 3Rs fitted to some extent Engelhardt ethical values. But the analysis also revealed some internal contradictions between the 3Rs and Engelhardt's ethical values. Although the 3Rs are still valuable tools in animal ethical evaluation, the present analysis suggests that some ethical issues still remain to be clarified.

An ethical analysis of the 3Rs

According to John Webster (1994), the use of animals in biomedical research (or any other research domain using animals as experimental subjects) entails ethical costs to the animal subjects, which consist mainly in suffering, pain, distress, infringement upon species typical behavior and death. In industrial countries, it is mandatory to assess ethical costs before any research project using animals can be carried out. Such an evaluation aims at minimizing costs to animals and at the same time at maximizing benefits (both in terms of scientific knowledge and quality of life) for both humans and animals. In order to carry out this cost-benefit analysis, local animal care and use committees (i.e., IACUC) rely on standards that have been referred to as the 3Rs (Russell & Burch, 1959). That is researchers must look for alternatives to animal use in research (i.e., Replacement), they must use the minimum number of animals (i.e., Reduction), and they must minimize the pain inflicted on animals (i.e., Refinement).

Even though the 3Rs are widely accepted as ethical standards, at least in Western societies (CCAC Guidelines 2000; NHMRC, 1997; Orlans, Beauchamp, Dresser, Morton & Gluck, 1998), and also taking into account the fact that alternatives to animal use is an expanding field of research (Balls, van Zeller, & Halder, 2000), which undoubtedly underlines the impact of the 3Rs, the ethical status of the 3Rs still remains to be clarified. Actually, the 3Rs were not derived from any ethical theory, but they represented an attempt to increase humanity to animal experimentation and at the same time to improve validity of scientific data (Russell & Burch, 1959). Given the controversy surrounding animal experimentation (Jasper & Nelkin, 1992; Regan, 1983; Rowan & Rollin, 1983; Singer, 1990) and the weight given to the 3Rs in animal ethical evaluation, it appears relevant to address the issue of the

ethical status of the 3Rs. More precisely, this article aims at providing an ethical analysis of the 3Rs through Engelhardt's bioethics theory (1998, 1995).

The 3Rs: historical context and definition

Russell and Burch published their landmark book “The Principles of Humane Experimental Technique” in 1959. It is generally agreed that it had little influence for decades after its publication (Festing, 1995). But it should also be remembered that their book came out during an era in which ethical concerns pertaining to animal experimentation were at an all time low (Loew, 1996). As already underlined, the 3Rs represented an attempt to provide humane treatment to animals used in experimentation and to secure scientific validity as well.

Humane treatment of animals originated in the late eighteen century when men having dominion (and power) over animals realized that those animals had to be treated properly (Smith & Boyd, 1991; Webster 1994). Basically, humane treatment meant lessening pain and fear inflicted on animals whatever they were used for. But it is in 1831 that Marshall Hall proposed guidelines and principles in order to ensure proper treatment to animals used in experimentation (see Smith & Boyd, 1991). Hall's principles insisted on the necessity to relate any experiment to a definite object, to lessen pain to animals used in experimentation, to avoid unnecessary repetition of the same experiment, and finally not to carry out experiments whenever observation could be used. These principles were actually a compromise between antivivisectionists and animal researchers, especially physiologists (Smith & Boyd, 1991).

In some ways Russell and Burch's 3Rs represented an extension of Hall's principles. However, Russell and Burch framed the 3Rs within the Darwinian approach and they based their argumentation on the most recent (at that time) empirical evidence regarding brain anatomy and both physiological and psychological processes, especially in vertebrates. In doing so, they alleged that pain could modify both the physiological and the psychological state of animals. As such, pain could be conceived of as a confounding variable that had to be eliminated in order to secure valid data. Hence, Russell and Burch ensured that humane treatment would be correlated with scientific validity. In doing so, they also found a way to reconcile researchers with procedures aiming at lessening pain inflicted on animals. At that time, such procedures were often viewed as an obstacle to carry out research (see Russell & Burch, 1959).

This way of thinking was in itself quite revolutionary for the times, as noted by Festing (1995). Russell and Burch proposed to achieve humane treatment of animals in the specific context of scientific experimentation by the use of the 3Rs, which are defined below.

Replacement. For Russell and Burch animal use ought to be replaced in two ways. The first is known as Absolute Replacement and the second is Relative Replacement. Absolute replacement is defined as:

“In absolute replacement, animals are not required at all at any stage. It follows from what has been said earlier that absolute replacement may be regarded as the absolute ideal”

(Russell & Burch, p. 70)

Relative Replacement is defined as:

“Replacement means the substitution for conscious living higher animals of insentient material. In relative replacement, animals are still required, though in actual experiment they are exposed, probably or certainly, to no distress at all” (Russell & Burch, p. 64).

The most obvious examples of Absolute Replacement are tissue culture, computers, the use of microorganisms, non-living physical and chemical systems and, of course, plants. Examples of Relative Replacement would be the substitution of primates by rats or mammals by fish or reptiles (Balls 1994; Smyth 1978). What follows from the definition of Replacement is that animals should only be used after a thorough search and rejection of all the alternative methods. Then, if the use of animals is deemed essential to the project, the researcher has to use the least sentient species to ensure valid results.

Reduction. The second principle is reduction:

“Reduction means reduction in the number of animals used to obtain information of given amount and precision” (Russell and Burch p. 64).

So, to properly reduce the number of animals needed in a particular research project, the researcher has to apply statistical methods to determine the minimum number of animals needed to reach statistical significance. This also means that to use the minimum number of animals one has also to assess the relevance and the quality of the research design (Festing 1995).

Refinement. Finally, the third principle is refinement:

“Refinement means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used” (Russell and Burch, 1959, p. 64).

Refinement encompasses every condition under which experimental animals can be put in. It includes first housing and caring of the animals, which must be done by experienced personnel. Next, come the experimental procedures themselves. It is the responsibility of every researcher to examine the manipulations that will be administered to the animals, to determine the risk factors regarding suffering and to try to minimize them. There should also be a concerted effort to provide analgesics whenever possible. Also, the animals should be humanely euthanized, that is, with the least amount of suffering.

In summary, the 3Rs encompass many dimensions such as planning, methods, purchasing, housing and caring of experimental animals. As such, they allow for good management practices and proper care of animals used in experimentation and, according to Russell and Burch (1959; see also Russell, 1998) they should be part of the evaluation of any research project involving animals.

An ethical theory: Engelhardt's Bioethics

Engelhardt (1998) has elaborated the steps toward an ethics encompassing human life, animal life and environment. Engelhardt derived his ethical concerns from both a secular and a pluralistic

point of view. In Engelhardt's theory (1998), nonmalevolence and beneficence are at the heart of any ethical concern for all organisms. To respect the former is to act in ways that would not be detrimental to organisms; while to adhere to the latter is to be good towards all forms of life. From these two principles are derived four node concepts or values from which norms can be defined.

The first value is reverence for life. This is an affirmation that life, in and of itself, is worthy of moral concern. This value touches upon other concepts such as beauty and respect. Here, moral concern is not channeled only through rational thinking but also through an appreciation of aesthetics about the diverse forms of life. If there ought to be reverence for life, it follows that both individuals and societies should set boundaries that cannot be crossed under any circumstances. In addition, these limits should be translated into ethical principles, laws and guidelines in order to make it possible to weigh some particular use of animals or ecosystems; so as to foresee the consequences of one's actions on those lives involved.

Stemming from reverence for life arises the second value, which states that life, in and of itself, has dignity. Each organism, no matter how small, is perceived as unique and as such worth respect. Engelhardt (1998) underlines that this value is problematic in its application because it assumes not only a dignity that might be violated but also an infringement upon a "legal condition". This creates some conceptual problems since animals and the environment have no legal rights, thus what could it mean to violate an organism's dignity if there are no rights? But basically, because animals cannot consent to anything we might inflict upon them, and because we admit that life itself is worthy of moral concern, then there should be an obligation to respect life and not to over-use animals for our own pleasures. This would be the minimal requirement to respect life and its dignity.

Third, if we are to respect other species and their dignity it follows that we should avoid inflicting them pain and suffering. Therefore, one major step towards nonviolence would be to determine the ways animals might suffer and to try to eliminate it. But as any physiologist will tell you there is a problem in defining precisely what is meant by "pain and suffering" (Rowan 1995). In addition, in every society there is an acceptance that some suffering and pain are necessary part of every being's life including humans. Thus what would constitute "needless suffering" remains open to discussion and begs to be defined. It follows from this that there is an acceptable threshold for every society that should not be crossed, although some would contend that these limits are still too permissive (Francione 1996).

The last and fourth value is biodiversity. Engelhardt (1998) points out that biodiversity is priceless and it stems from the value of respect for life. Because the web of life is characterized by interconnectedness, we have a moral obligation to protect endangered species and we are responsible for the environment's health. Therefore, each and every society has to put forward the criteria by which some species will (or ought to) be protected (Engelhardt 1998); though Engelhardt acknowledged that it is impossible to save all species from extinction.

Engelhardt's theory and the 3Rs

The first step in analyzing the 3Rs from Engelhardt's bioethics theory is to examine to what extent Replacement, Reduction and Refinement are in agreement with Engelhardt's four values.

Absolute replacement is certainly in a close correspondence with all four values of Engelhardt's bioethics theory. In looking for absolute replacement one would necessarily respect animals' life and dignity. By doing so, there will not be any suffering inflicted to animals. This will also respect biodiversity, as long as the alternative method is not harmful to the environment. Relative replacement is also a way to respect life and to reduce suffering. However, that would necessarily benefit only to the species being replaced, not to the new target species. Hence, one has to restart the whole process again with the new target species. The way to solve this problem within the 3Rs' approach is to replace a species by a less sentient one. However, this is not without any problem. First, if one is to respect life and dignity, the life and dignity of the species used as substitute are violated. Second, the "less sentient" argument is based on scientific knowledge, as what was suggested by Russell and Burch (1959). This argument assumes that the less the brain is complex the less the animal will suffer. However, Sherwin (2001) has recently challenged this argument in pointing out that invertebrates, which are usually endowed with a reduced capacity to experience suffering, exhibit similar behavioral responses in terms of learning and memory than those exhibited by vertebrates. Such behavioral responses are usually associated with a capacity to experience suffering in vertebrates. Finally, Carruthers (2004) has recently argued that subjective experience is not necessarily a prerequisite to pain and suffering.

Reduction also fits with respect for life because in using the minimal number of animals researchers will avoid to unduly use animals. However, this leaves open the issue of which individual will be chosen (i.e., will be used as an experimental subject) and which one will not be chosen (i.e., will stay alive).

Finally, refinement is in agreement with nonviolence. Refinement aims at decreasing and/or eliminating suffering regarding any procedure that could be administered to animals. Post surgery administration of painkillers is one example among others. However, as such this principle can contradict the value of respect for life as one can eliminate suffering and the same time put the animal in a situation in which it will die (as it is often the case in animal experimentation).

But Engelhard's theory calls for a more elaborate analysis than just a simple mapping of each of the 3Rs onto each one of the four values. Engelhard's theoretical framework takes into account the interconnectedness of the web of life and it also requires social consensus regarding ethical norms. In this sense, one must address the issue of the contexts in which the 3Rs are used.

First, in what can be referred to as the immediate context, the 3Rs are used within the context of ethical animal evaluation. That is, as proposed by Russell and Burch (1959), they are part of the evaluation of any research project involving animals used as experimental subjects. Animal ethical evaluation is a complex process that entails both ethical judgment and scientific reasoning (Houde, Dumas & Leroux, 2003). As such, the 3Rs are bound to the basic premise underlying animal ethical evaluation which states that what it is not scientifically valid cannot be ethical. Accordingly, each research project involving animals as experimental subjects has to be assessed from a scientific point of view regarding crucial elements such as the rationale underlying the project, the research hypotheses, the experimental design and so on. This means that scientific validity is not strictly limited to the elimination of pain as a confounding variable. This certainly adds to the ethical dimension of the 3Rs.

Second, in the extended context, the 3Rs are part of the social phenomenon that we refer to as animal experimentation. How does the 3Rs relate to the numerous issues linked to animal experimentation? We can hardly provide a definitive answer to this question. However, at first glance, there seems to be some major limitations. For example, one can provide conditions that will satisfy the 3Rs requirements, but at the same time use as experimental subjects animals whose genotype have been modified. Modifying the genotype of an animal certainly raises issues relevant to Engelhardt's ethical values regarding respect of life and dignity (see also Carbone, 2004 and Fleming, 2004 on this point). But the 3Rs remain silent on this point.

General discussion

Russell and Burch's 3Rs (i.e., Reduction, Replacement and Refinement) are widely accepted as ethical standards in Western societies regarding animal ethical evaluation. However they were not derived from any ethical theory. The present article aimed at providing a (preliminary) analysis of the ethical status of the 3Rs through Engelhardt's bioethics theory. The analysis revealed that the 3Rs fitted to some extent Engelhardt bioethics theory. Indeed relying on alternative methods to animal use in experimentation, making an effort to reduce the number of animals used in experimentation and refining procedures so that pain is eliminated is in agreement with ethical values such as reverence for life, dignity, painless treatment and biodiversity.

However, the analysis also revealed some contradictions regarding the 3Rs. However people using the 3Rs do not necessarily conceive these three principles as contradicting each other. People using the 3Rs do not necessarily conceive the 3Rs as contradicting each other. This is so because when

evaluating research protocols members of institutional animal care verify separately if each principle has been satisfied. committees verify each principle separately. Contradictions arose because in analyzing the 3Rs we had to take into account the four ethical values in Engelhardt bioethics theory. Another reason that might account for the fact that people using the 3Rs do not seem them as contradicting each other is that these principles focus on a single dimension, that is pain;. Since the original proposal in the late fifties, scientific knowledge and technology expanded in an exponential way so that focusing on a single dimension (i.e., pain) may set some limitations to the ethical status of the 3Rs. It is not to say that the 3Rs are of no practical value in animal ethical evaluation. Quite the opposite, and as such they are still valuable tools in evaluating research protocols using animals as experimental subjects (see Houde, Dumas & Leroux, 2003). But as suggested by the present analysis, some ethical issues still remain to be clarified.

Finally, Engelhardt (1995) acknowledged that animals should not be reduced to "things". Indeed, he explicitly (Engelhardt, 1995) stated that we have the duty to take into account the pain and suffering of animals when applying the principle of beneficence. In this sense, one can ask to what extent the 3Rs can be conceived of as ethical norms within Engelhardt's theory. So let's assume that the 3Rs are ethical norms, the main issue would be how to solve the contradictions that were derived from our analysis. There is no clear answer to this question. Beauchamp (1997) pointed out that one problem with Engelhardt theory is that it is weak in normative content. That is principles like beneficence (and ethical values) are far too general so that they can be specified in many ways, even in "competing" ways (see Beauchamp, 1997, p.98). In addition, according to Engelhardt each community must address such issues which would lead to community relativism. That is how can we proposed principles if each community can set its own ethical norms. Beauchamp (1997) also underlined that

this is a real problem when one has to deal with complex multicultural societies as do people using the 3Rs. In some way, a consensus can certainly be reached within the scientific community but it remains to be seen how such a consensus can be reached within many societies. Nonetheless, Engelhardt bioethics theory proved to be heuristic in providing a theoretical framework to address the issue of the ethical status of the 3Rs.

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