

## Opinion

# Principles and Paradigms Used in Human Medical Ethics Can Be Used as Models for the Assessment of Animal Research

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The preparation of the Obrink Memorial Lecture for presentation to the Scandinavian Association of Laboratory Animal Science (1) provided me with an impetus for further reading and thinking about IACUC review of research protocols using animals. One of the primary responsibilities of laboratory animal specialists and comparative medicine scientists is to bridge the worlds of the investigator, the bioethicist, and the public; therefore, I welcome the opportunity to share the essence of the Obrink Memorial Lecture with colleagues in AALAS. My current approach to the assessment of protocols is based on a "definition" of ethics and morals, a basic set of principles, a casuistry grid, and the application of the principles and grid to human medical problems as a model (2).

It is generally agreed among ethicists that ethics, rather than a moral point of view, be used to determine whether a particular use of animals is proper. This implies a difference between *ethics* and *morals*. Because both terms are concerned with the rightness or wrongness of an action, the traditional definitions are synonymous. However, there is a distinction between them. *Morals* connotes one's own beliefs of what is right and what is wrong, while *ethics* connotes a theoretical assessment tool by which one can decide about the appropriateness of a given act. The assessment of the ethics of an act, therefore, requires, i) a basic set of principles and ii) an agreed-upon, systematic consideration of a set of circumstances rather than the imposition of one's own moral beliefs.

**Basic principles for the human model: The Belmont Report.** The National Commission for the Protection of Human Subjects established conditions for the use of human subjects that recognize and respect several interests: respect for the autonomy of humans, respect for the freedom of inquiry, the avoidance of needless pain, injury, and humiliation; and the maximization of and equity in the distribution of social benefits. Their report is commonly referred to as The Belmont Report (3), because one of their meetings was held at the Belmont House of the Smithsonian facility at Elkridge, Maryland. These conditions are founded on three ethical principles:

- respect for person
- justice
- beneficence (marked by performing kind or charitable acts)

**Basic principles for the assessment of biomedical research using animals: The Sundowner Report.** While the

Belmont Report identified explicit principles underlying the ethical evaluation of research involving human subjects, only implicit principles in the *Guide* and the Animal Welfare Act were available for animals in 1995. A committee was appointed by the National Aeronautics and Space Administration (NASA) to address questions about the use of rhesus monkeys in space for the Bion 11 and Biocosmos projects and to develop explicit principles for the ethical evaluation of research involving animals (4). The committee's report, using the Belmont Report as a model, is commonly called the Sundowner Report, after the location of their meeting in California.

The Sundowner Report was adopted by NASA to guide careful and considered discussion of the ethical challenges that arise in the course of biomedical research using animals and provide a framework within which challenges can be rationally discussed. The passage below from the NASA document announcing adoption of the principles (5) provides some context as to the basis and the use of those principles.

Introduction: A strong allegiance to the principles of bioethics is vital to any discussion of responsible research practices. As reflected in the considerations of the National Commission for the Protection of Human Subjects, "scientific research has produced substantial social benefits... [and] some troubling ethical questions" (The Belmont Report, 1979). The Belmont Report identified the key fundamental principles underlying the ethical evaluation of research involving human subjects. Similarly, the principles governing the ethical evaluation of the use of animals in research must be made equally explicit.

It is generally agreed that vertebrate animals warrant moral concern. The following principles are offered to guide careful and considered discussion of the ethical challenges that arise in the course of research, a process that must balance risks, burdens, and benefits. NASA will abide by these principles as well as all applicable laws and policies that govern the ethical use of animals. It is recognized that awareness of these principles will not prevent conflicts. Rather, these principles are meant to provide a framework within which challenges can be rationally addressed.

Basic Principles: The use of animals in research in-

Table 1. Jonsen's Casuistry Grid for Human Medical Ethics

MEDICAL INDICATIONS	PATIENT PREFERENCES
<ol style="list-style-type: none"><li>1. What is a patient's medical problem? history? diagnosis? prognosis?</li><li>2. Is problem acute? chronic? critical? emergent? reversible?</li><li>3. What are goals of treatment?</li><li>4. What are probabilities of success?</li><li>5. What are plans in case of therapeutic failure?</li><li>6. In sum, how can this patient be benefitted by medical and nursing care, and how can harm be avoided?</li></ol>	<ol style="list-style-type: none"><li>1. What has the patient expressed about preferences for treatment?</li><li>2. Has patient been informed of benefits and risks, understood, and given consent?</li><li>3. Is patient mentally capable and legally competent? What is evidence of incapacity?</li><li>4. Has patient expressed prior preferences, e.g., Advance Directives?</li><li>5. If incapacitated, who is appropriate surrogate? Is surrogate using appropriate standards?</li><li>6. Is patient unwilling or unable to cooperate with medical treatment? If so, why?</li><li>7. In sum, is patient's right to choose being respected to extent possible in ethics and law?</li></ol>
QUALITY OF LIFE	CONTEXTUAL FEATURES
<ol style="list-style-type: none"><li>1. What are the prospects, with or without treatment, for a return to patient's normal life?</li><li>2. Are there biases that might prejudice provider's evaluation of patient's quality of life?</li><li>3. What physical, mental, and social deficits is patient likely to experience if treatment succeeds?</li><li>4. Is patient's present or future condition such that continued life might be judged undesirable by them?</li><li>5. Any plan and rationale to forgo treatment?</li><li>6. What plans for comfort and palliative care?</li></ol>	<ol style="list-style-type: none"><li>1. Are there family issues that might influence treatment decisions?</li><li>2. Are there provider (physicians and nurses) issues that might influence treatment decisions?</li><li>3. Are there financial and economic factors?</li><li>4. Are there religious, cultural factors?</li><li>5. Is there any justification to breach confidentiality?</li><li>6. Are there problems of allocation of resources?</li><li>7. What are legal implications of treatment decisions?</li><li>8. Is clinical research or teaching involved?</li><li>9. Any provider or institutional conflict of interest?</li></ol>

volves responsibility, not only for the stewardship of the animals but to the scientific community and society as well. Stewardship is a universal responsibility that goes beyond the immediate research needs to include acquisition, care and disposition of the animals, while responsibility to the scientific community and society requires an appropriate understanding of and sensitivity to scientific needs and community attitudes toward the use of animals.

Among the basic principles generally accepted in our culture, three are particularly relevant to the ethics of research using animals: respect for life, societal benefit, and non-maleficence.

### 1. Respect for Life

*Living creatures deserve respect.* This principle requires that animals used in research should be of an appropriate species and health status and that the research should involve the minimum number of animals required to obtain valid scientific results. It also recognizes that the use of different species may raise different ethical concerns. Selection of appropriate species should consider cognitive capacity and other morally relevant factors. Additionally, methods such as mathematical models, computer simulation, and in vitro systems should be considered and used whenever possible.

### 2. Societal Benefit

*The advancement of biological knowledge and the improvements in the protection of the health and well being of both humans and other animals provide strong justification for biomedical and behavioral research.* This principle entails that in cases where animals are used, the assessment of the overall ethical value of such use should include consideration of the full range of potential societal goods, the populations affected, and the burdens that are expected to be borne by the subjects of the research.

### 3. Non-maleficence

*Vertebrate animals are sentient.* This principle entails that the minimization of distress, pain, and suffering is a moral imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in humans may cause pain or distress in other sentient animals.

I submit for your consideration that fundamental principles underlying the ethical evaluation of research with animals have been developed. The Sundowner Principles are an extension and modification of the Belmont Principles for human medical ethics and provide a foundation for the ethical evaluation of research involving animal subjects.

**Committee Review and Decision Paradigm: "Casuistry"—the application of general principles of ethics in the determination of right and wrong.** Casuistry has its origins with Catholic theologians from the fourteenth century onward and their use of moral rules to address ethical issues. In *Clinical Ethics*, the Jonsen casuistry grid for reviewing human medical ethics (Table 1) is applied as an assessment tool to complement the principles in the Belmont Report for medical interventions with patients (2). Is there a single assessment tool that can be applied to the use of laboratory animals in biomedical research? It is my perception that most, if not all, members of committees evaluating research projects using animals would answer "no." However, at a workshop in Seattle, Jonsen presented a casuistry grid (Table 2) that could be applied to the use of animals in research (6).

In my Obrink Memorial Lecture (1), a genetic engineering project in mice to develop an animal model for Parkinson's disease in humans was summarized and the use of the paradigm was illustrated; as in the consideration of medical ethics, circumstances will dictate which issues need to be explored in greater detail. In addition, a surveillance system for early identification of unanticipated adverse effects and a phenotyping protocol were described (Table 3) (7). A review of *Clinical Ethics* (2), is recommended for examples of the application of the process for dilemmas in human medicine.

**Table 2.** Jonsen's Casuistry Grid as a Model of Decision Paradigms Applied to Experimental Animal Issues**ALTERNATIVES**

1. 3-R's—refinement, reduction, replacement.
2. PI search failed to identify non-animal methods.
3. In vitro pilot studies.

**EXTERNAL FACTORS**

1. Distress of procedures to personnel.
2. Symbolic or sentimental value of species to people.
3. Sentience and scarcity of species.
4. Status of transgenic animals.
5. Importance of condition studied.

**CONTRIBUTION TO SCIENTIFIC KNOWLEDGE**

1. Adherence of animal procedures to standards.
  - a. Does PI justify departures from standards?
  - b. Are sample sizes appropriate?
  - c. Is survival surgery aseptic?
  - d. Antibody production conform to guidelines?
  - e. Proper blood sampling protocol?
  - f. Proper facilities & equipment etc.
2. Payoff and benefit to society.
3. Will scientific understanding of problem studied be advanced?
4. Training and qualifications of personnel.
5. Presence or absence of peer review.

**QUALITY OF LIFE**

1. Pain, distress, discomfort, & suffering.
2. Monitoring for signs of pain.
3. Anesthesia, analgesia.
4. Deprivation (food, water, social).
5. Euthanasia, death as an end point.
6. Application of noxious stimuli (behavior testing, toxicity).
7. Provision of adequate housing, veterinary care.
8. Treatment of controls.

**Table 3.** Sample Phenotyping Protocol

1. Morbidity
  - a. Fetal death
  - b. Lifespan
2. Fertility (Litter size at birth and weaning)
3. Development:
  - a. Birth weight
  - b. Growth rate
  - c. Hair growth
  - d. Development of neonatal reflexes
  - e. Age at incisor eruption
  - f. Age eyes & ears open
  - g. Age at standing and walking
4. Clinical parameters:
  - a. Physical exam for malformations
  - b. Coat condition
  - c. Nasal or ocular discharge
  - d. Hemogram
  - e. Serum chemistry profile
  - f. Tumor development
5. Simple behavioral parameters:
  - a. Posture, climbing, and locomotion
  - b. Eating and drinking
  - c. Grooming
  - d. Activity level, exploration
  - e. Alertness
  - f. Aggression
  - g. Twitches, tremors
  - h. Stereotypic behaviors
  - i. Righting
  - j. Auditory startle
  - k. Seizures
  - l. Reflexes
6. Necropsy and Histology
7. Specialized testing:
  - a. T and B cell function
  - b. Cytokine profile
  - c. Pathogen susceptibility
  - d. Complex behavioral testing
  - e. Learning testing

While the "3R's," i.e., reduction, refinement, and replacement (8), has been a useful concept, it does not appear applicable to many genetic engineering studies with animals; for example, such experiments have resulted in an increase in animal use in many institutions instead of a reduction. Advantages of the explicit principles in the Sundowner Report in conjunction with a casuistry grid include the precedent of the paradigm in addressing ethical problems in human medicine and the balance it brings by including the scientific contribution of a project. Spinelli has made minor modifications to the grid proposed by Jonsen (9), and further modifications may be made as experi-

ence with the grid is acquired in the review of protocols for animal use.

A decisional model has also been described by Stafleu for use by committees evaluating animal experiments which embodies the principles in the Belmont Report (10). To solve ethical dilemmas, decision making rules and numerical values are assigned and compiled, and the scores used as a basis for approving or disapproving a research proposal. The quantitative aspects of this paradigm, or modifications of the strategy, may be useful for individuals on a review committee who have difficulty deciding on approval or disapproval of a project.

In conclusion, I submit for the reader's consideration that the use of a structured approach and basic principles which have been used successfully to guide physicians in making decisions about medical problems can be used as a model for the review and decision making about research projects involving animals. The application and further development of this paradigm provides laboratory animal scientists an opportunity to use their training, experience, and position to address the concerns of animal research, bioethics, and the public good.

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