Responsible Use of Animals for Research

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Responsible Use of Animals for Research

- History of animal use for research
- Attitudes and philosophical perspectives
- Animal use regulations (protection)
- The concept and practice of the 3 R’s of animal use for research
- Some hot button items – tough ethical questions/issues
Animal Use by Humans is Ancient

- Dogs were domesticated 15,000 years ago and livestock about 10,000 years ago.
- Types of Animal Use is Wide-Ranging
  - Food
  - Clothing
  - Companions
  - Work
  - Entertainment
  - Research
History of Animal Use in Research

• Aristotle (384-322 BC)
  – Characterized as the founder of Biology
  – The first to have made dissections that revealed internal differences among animals.

• Erasistratus (304-258 BC)
  – established in pigs that the trachea was an air tube and the lungs were pneumatic organs.

• Galen (130-200 AD)
  – used apes and pigs to prove his theory that veins carry blood rather than air
History of Animal Use in Research

- Sir William Harvey (1628)
  - published his great work on the movement of the heart and blood in animals.

- Stephen Hales (1700’s)
  - reported the first measurement of blood pressure using a horse as his subject

- Claude Bernard (1865)
  - published *An Introduction to the Study of Experimental Medicine*
Contributions of Animal Research to Medical Science

- Every major medical advance in the last 100 years has involved animal research.
- 68 Nobel Prizes in Medicine in the last 101 years involved animal research.
- Antibiotics, vaccines, surgical treatments, drug testing, organ transplantation, and cancer therapies were all developed through animal research.
Specific Medical Milestones

Infectious Diseases –

- Therapies for treatment and prevention of polio, smallpox, rubella, pertussis, measles, mumps, leprosy, tetanus, TB, and diphtheria all were pioneered with experiments involving mice, rats, chickens, dogs, and monkeys.

- Development of antibiotics

Organ Transplantation –

- Kidney, lung, and liver transplant techniques as well as the development and testing of anti-rejection drugs.
Specific Medical Milestones

Cancer –

- rats have been the major animal used in toxicology screening of carcinogenic compounds.

- development and testing of new cancer treatments (drugs, radiation, gene therapy) is routinely conducted in animals.

Cardiovascular –

- development of the techniques of cardiac catheterization, open heart surgery, cardiac pacing
Specific Medical Milestones

Treatment and Understanding of Diseases Such as:
- diabetes mellitus
- epilepsy
- hemophilia
- Asthma
- Hypertension

Development of Surgical Techniques –
- orthopedic procedures and prosthetics
- laparoscopic surgical techniques
Benefits to Animals

• Vaccines for rabies, distemper, parvovirus, feline leukemia

• Immunizations for cholera in hogs, encephalitis in horses, brucellosis in cattle

• Treatment for heartworm, intestinal parasites

• Nearly every medical procedure now done on humans is being used or studied for use at the nation’s companion animal medical centers.
# Animal Use By Humans

**Number of Animals Used Annually in U.S.**

- **Food**: 6,086** (96.5%)**
- **Hunting**: 165 (2.6%)
- **Killed in Pounds**: 27 (0.4%)
- **Research and Teaching**: 20 (0.3%)
- **Fur Garments**: 11 (0.2%)
- **Total**: 6,309 (100%)

*From Nicoll and Russell, 1990*

**Expressed in millions**
Animal Use in Research

**U.S. Data Collection (Orlans 1993):**
- basic science ~40%
- drug development and eval, and toxicity assessment ~26%
- product safety testing (other than drugs) ~20%
- education ~7%
- other purposes ~7%

**Netherlands Data Collection (Gov’t 1987):**
- fundamental research ~42%
- vaccine and drug production and testing ~47%
- toxicity testing ~6%
- education and training ~4%
- other purposes ~1%
The Animal Research Dilemma

Despite the good that has come from animal research, there is an ethical cost. Research using animals has saved human lives, reduced human suffering, and increased scientific understanding, however, most animals used in research are euthanized at the end of the experiment.

*Are the costs ethically acceptable in order to achieve medical progress?*
Wide-Ranging Attitudes Toward Animal Use

- **Animal exploitation (Abuse) -**
  - Humans have absolute dominion over animals.

- **Animal Use –**
  - Animals can be used to meet human needs; can police ourselves.

- **Animal Welfare –**
  - Limits should be set on animal use for human purposes.

- **Animal Rights –**
  - Animals have intrinsic rights that should be guaranteed just as ours are.

- **Animal Liberation –**
  - Eliminate animal use completely.
The Debate: Philosophical Views

• “Animal Rights” versus “Animal Welfare”

• Descartes – defended use of animals in experiments and argued that animals lack the ability to reason and think and are therefore similar to a machine.

• Utilitarianism (Jeremy Bentham, 18th century philosopher)
  – Consequences determine what is right.
  – An action is right if and only if it produces a better balance of benefits and harms than available alternatives
  – Ends do not justify the means.
  – Pleasure and pain are considered interests
  – Animals can have interests since they can feel pleasure and pain
  – “The question is not, Can they reason? But, Can they suffer?”
The Debate: Philosophical Views

• Peter Singer – *Animal Liberation (1975)*
  - Popularized the term *speciesism* – discrimination against nonhuman animals simply because they are of another species when that fact is irrelevant to the value at stake (such as pain and suffering).

• Deontology – (Rights Based Theory)
  - Consequences are not the only factor in moral evaluation.
  - Some actions might be right even if the consequences are not good, and other actions are ethically wrong even if the consequences are good.
  - Certain rights can not be overridden.
The Debate: Philosophical Views

• Contractualism
  – Moral obligations are the outcome of contracts between members of society
  – Animals cannot enter into contracts but might be the benefactors of such contracts.

• Humean Ethics (David Hume, British Philosopher)
  – Ethics is not based on abstract rationalism but must involve emotions, including sympathy and empathy.
  – We can have duties toward animals based on our emotions, independent of their rights.
A right is a potential claim that one party exercises over another. 
Those who hold rights must be able to understand and self-legislate. 
Animals therefore can not have rights. 
Hence in research, what do we do? We can not violate their rights, because they do not have any. 
But… we are obligated to treat animals humanely, just as adults treat children, and teachers do students.

To treat animals humanely is not to treat them as humans!
The Public Perspective

*Parents Magazine* survey (1990)

- 80% respondents agreed with the statement that animals have rights that should limit how humans use them.
- Majority believed that certain activities were wrong and should be illegal
- 63% - killing animals to make fur coats should be prohibited
- 58% - using animals for cosmetic research should be prohibited
- 85% agreed it is acceptable to kill animals for food
- 58% approved of use of animals for research
National Science Board Surveys of Public Attitudes toward Animal Research

Survey participants were asked to express their level of agreement or disagreement with the statement: “Scientists should be allowed to do research that causes pain and distress to animals like dogs and chimpanzees if it produces new information about human health problems.”

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F. Barbara Orlans. Sci Am (1997): “It is possible to be both pro research and pro reform. Animal liberators need to accept that animal research is beneficial to humans. An animal researchers need to admit that if animals are close enough to humans that their bodies, brains, and even psyches are good models for the human condition, then ethical dilemmas surely arise in using them. But the moral burden is not for scientists alone to bear. All of us who use modern medicine and modern consumer products need to acknowledge the debt we owe to our fellow creatures and support science in its quest to do better by the animals.”
Protection for Animal Subjects of Research

- Animal research is highly regulated.
- Current Laws, Standards, and Accrediting Agencies –
  - US Gov’t Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training
  - Animal Welfare Act and Regulations (AWA)
  - PHS Policy on Humane Care and Use of Laboratory Animals (PHS)
  - Guide for the Care and Use of Laboratory Animals
  - Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC)
Development of the Current Laws and Standards for Animal Protection

• 1950 – formation of the Animal Care Panel (ACP)
• 1953 – development of the Institute of Animal Resources
  – Renamed the Institute of Laboratory Animal Resources (ILAR). ILAR is a unit of the National Research Council of the National Academy of Sciences, a private nonprofit organization that exists to provide expert scientific advice to the gov’t and the public.

ILAR mission – to develop guidelines and to disseminate information on the “scientific, technological, and ethical use of animals and related biological resources in research, testing, and education.” (NRC 1996)
Development of the Current Laws and Standards for Animal Protection

• 1963 – NIH contracted with ILAR to offer guidance for awardee institutions concerning the care, housing, and husbandry that should be provided for vertebrate animals involved in research.
  – The *Guide* is recognized as a worldwide standard for laboratory care and use programs.
  – The *Guide* – provides guidelines for scientifically, technically, and humanely appropriate animal care and use.
Development of the Current Laws and Standards for Animal Protection

• 1966 – Laboratory Animal Welfare Act was passed requiring registration of all animal laboratories and licensing of all dealers. Originally designed to prevent the theft of dogs and cats, and covered only the care and transportation of animals.

• 1970 – Renamed the Animal Welfare Act (AWA) and expanded to include all warm-blooded species.
  – Has been amended several times; now provides detailed protection for laboratory animals.
  – addresses broad aspects of use and justification of the use of animals in research.
Development of the Current Laws and Standards for Animal Protection

- **AWA (1985 amendment):**
  - requires that each facility conducting animal research establish IACUCs.
  - addresses psychological well-being of non-human primates, exercise regulations for dogs.
  - specifies that pain and distress must be minimized in experimental procedures.
  - defines practices that are considered to be painful.
  - requires that alternatives to such procedures be considered by the PI.
Development of the Current Laws and Standards for Animal Protection

• PHS Policy on Humane Care and Use of Laboratory Animals (PHS Policy)
  – Revised in 1985 to address concerns of lack of adequate resources, administrative support, and authority for institutional veterinarians and their staff.
  – Required ID of “institutional official” to be held accountable for laboratory animal program
  – Requires establishment of IACUC at awardee institution
  – Semiannual inspection of all animal facilities
  – Occupational health program for all persons who have contact with lab animals
Institutional Animal Care and Use Committee

• Federal law stipulates that every institution must have an official committee to review all care and use of animals in research. This committee’s responsibilities include:
  – Review and approve all animal research procedures.
  – Inspecting animal care and use facilities (min. of every 6 mo)
  – Evaluating the animal care and use program (min. of every 6 mo)
  – Investigate concerns regarding animal research activities.

• Federal law requires that Committee membership include at the minimum:
  – A laboratory animal veterinarian
  – A researcher who uses laboratory animals
  – A non-scientist
  – A member of the public who is not affiliated with the institution
The Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC)

- international private nonprofit organization
- mission is to promote the highest of standards of laboratory animal care.
- qualifications for AAALAC accreditation are stringent and depend on meeting the provisions of the AWA, the PHS Policy, and the Guide.
- each institution evaluated every 3 years.
- private foundations and gov’t funding agencies regard AAALAC accreditation as evidence of commitment to a program of excellence in animal care.
- in some ways analogous to JCAHO
U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training – (9 Basic Principles)

- **Animal Transport** - The transportation, care, and use of animals should be in accordance with the AWA and other applicable Federal laws, guidelines, and policies.

- **Judicious Use of Animals** - Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

- **Alternative Methods** - The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.
U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training – (9 Basic Principles)

- Minimization of Pain & Distress
- Use of Appropriate Sedation, Anesthesia, and Analgesia
- Euthanasia - Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
- Animal Care - The living conditions of animals should be appropriate for their species and contribute to their health and comfort.
U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training – (9 Basic Principles)

• **Qualifications of Research Personnel & Provisions for Training** - Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals.

• **Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned, but should be made, with due regard to the Principle of Judicious Use of Animals, by an appropriate review group such as an IACUC.**
The Underpinning for the Laws and Standards are the 3 R’s of Animal Research

Underlying Concept/Goal: Animals should not be unnecessarily burdened!

• **Reduce** the number of animals used
• **Refine** the way experiments are carried out
• **Replace** animal experiments with non-animal techniques
The 3 R’s of Animal Research

Reduction – 3 primary methods

• Maximize the data gained from an individual animal (animal sharing)
• Avoid duplicating prior research unnecessarily
• Use sound statistical methods and study design
• Use better quality animals
The 3 R’s of Animal Research

Replacement

- Replace animals with in vitro models, computer models, when appropriate.
- Replace vertebrate animals with less sentient animals when possible.
The 3 R’s of Animal Research

Replacement

Several Centers/Foundations Dedicated to the Development and Promotion of Alternative Methods:

- Alternatives to Animal Testing/National Library of Medicine/NIH
- Johns Hopkins University Center for Alternatives to Animal Testing
- Interagency Coordinating Committee on the Validation of Alternative Methods (CCVAM)
- Institute for In Vitro Studies
- University of California Alternatives to Animal Testing
- Nat’l Inst of Environmental Health Sciences (NIEHS)
- European Center for Validation of Alternative Methods
- Fund for the Replacement of Animals in Medical Experiments (FRAME) in Great Britain
The 3 R’s of Animal Research

**Refinement** – research should be designed to minimize pain and distress.

– 4 General Categories of Refinement:
  - decreased invasiveness
  - improved instrumentation
  - improved control of pain
  - improved control of techniques
The 3 R’s of Animal Research

Refinement cont’ed

- Specific Refinement Opportunities:
  - Pain-relieving medications
  - New diagnostic and therapeutic techniques –
    - i.e. use of sophisticated imaging equipment to replace invasive procedures; blood and sampling techniques that allow easier collection and the processing of smaller sample sizes
  - Environment factors - relieve boredom; avoid stressful stimuli
  - Humane endpoints – establishment of the earliest possible humane endpoint consistent with research design
Stress and Distress in Laboratory Animals

• **Stress** – the biological response an animal exhibits in an attempt to cope with threats to its homeostasis (Stokes, 2000)

• **Stressors** – threats to homeostasis
  – physical, environmental, or psychological in origin
  – When an animal responds to a stressor in an adaptive way, the animal returns to a state of comfort.
• If animal is unable to completely adapt to a stressor → state of **DISTRESS** develops.
• **Distress** encompasses many negative psychological states:
  – Fear, pain, malaise, anxiety, frustration, depression, and boredom
  – Manifest as maladaptive behaviors – i.e. abnormal feeding or aggression, hypertension, immunosuppression
  – Inhumane procedures are those which drive the animal’s mood down toward these points.
Stress and Distress in Laboratory Animals

• **Non-Humans:**
  – At any given moment a lower vertebrate is in a particular mood, which restricts its scope of attention (Baerends, 1955; Russell 1954)
  – Can only be aware of, or react to, limited features of its internal and external environment.
  – Can not distract itself – analogous to a neurotic human with an unpleasant preoccupation

• **Humans:**
  – Can control the direction and focus of our attention
  – Can distract ourselves
Animal Research and Painful Procedures/Conditions

• Fundamental to the relief of pain, investigator must be able to recognize the clinical signs.
• There are some motor behaviors and physiologic responses to pain that are similar to the human response.
  – i.e. simple withdrawal reflexes; vocalization and escape; learned behaviors such as pressing a bar to avoid further exposure to noxious stimuli
• There are also species specific behaviors.
• It is your duty as an investigator to educate yourself.
Animal Research and Painful Procedures/Conditions

• US Gov’t Principles: “.........Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.”

• Acceptable levels of noxious stimuli – those that are well tolerated and do not result in maladaptive behavior.

• Pain threshold – the stimulus level at which pain is first perceived.

• Pain tolerance – the highest intensity of painful stimulation that an animal will voluntarily accept; as intensity of stimulus approaches the tolerance level, the animal’s behavior will become dominated by attempts to avoid or escape the stimulus.
Some Hot Button Issues

Pain Research

• Standards require that pain be relieved.
• To study pain and its treatment, it must be induced.
• General Guidelines (Dresser R. Rutgers Law Review 1988)
  – Any painful stimuli should be kept well below the animal’s pain tolerance threshold
  – Animals should be given control over stimulus intensity and duration by enabling them to terminate or escape it
• International Assoc. of Study of Pain – where possible, the investigator should first try out on him/herself any painful stimulus to be given to an animal.
Some Hot Button Issues

Studies that result in end stage illness or debilitation

• In most research, animals do not become clinically ill. In some research, however, clinically significant disease develops.

• Examples include:
  – Tumor studies
  – Sepsis
  – Burns
  – Hybridoma production
Some Hot Button Issues

Alternatives to end stage illness, debilitation, or death as an endpoint:

Develop a contingent experimental endpoint to signal euthanasia.

Ideal endpoints –

• can be used to end a study before the onset of pain and/or distress without jeopardizing the study’s objectives.

• reflect actual or imminent deterioration of an animal’s condition.

• are easy to assess
Good science and good animal care are inseparable. Stressed or mistreated animals are not good research subjects.
Issues to Assess Prior to Using Animals in Any Research Project:

• How many people or animals will the project benefit?
• How serious of a problem does this research address?
• What are the present or projected costs and burdens of the disease/problem to the economy, society, and the health care system? Is this study justified?
• Is there good scientific basis for the project? Are the scientific methods sound and well-developed? Is the proposed animal model the most appropriate?
• Have alternatives to animal use been considered?
• And always remember the 3 R’s
The Case of the Swimming Rat

**Purpose:** An investigator proposes to study the changes in cardiac muscle in rats subjected to exercise induced cardiovascular fitness.

**Methods:**

- Forced swimming of rats in a shallows tank filled with fresh thermo neutral water.
- Incremental increases in exercise intervals, starting at 10 minutes and gradually increasing to goal of 2 hours of continuous swimming.
- Experience of other investigators demonstrates that not all rats can achieve the 2-hour goal. Unsuccessful rats will drown.
The Case of the Swimming Rat

Is this OK?

NO!!! Violates the “minimization of pain and distress” principle and the principle that animals should be euthanized to avoid suffering and distress.

If not, how might this study design be modified?

Develop a mechanism to identify and rescue rats that are in danger of drowning.
The Case of the Septic Rat

**Purpose:** An investigator wants to study the effect on mortality of a new antibody in the treatment of sepsis.

**Methods:**

- Sepsis model – cecal ligation and puncture
- One group of animals treated with standard antibiotics and the new Drug X. Another group treated with standard antibiotics and placebo.
- Outcome measure is mortality at 96 hours.
The Case of the Septic Rat

Are there any problems with this protocol?

Yes. Need to consider developing and/or selecting a humane endpoint at which the animals can be euthanized?
The End