Chapter 2
Introduction

Donahue: ***What doesn't feel pain? When do you stop feeling pain? Does a frog feel pain?***

McArdle: Yes.

Donahue: ***Frogs feel pain? . . . now what about laboratory high school? You remember, you had to dissect the frog? . . . Should we eliminate that? How about fishing? . . . how about baiting a hook with a worm? IS that fair? In other words, where do we stop?***

McArdle: ***You bring up fishing and I think that's a good point. I used to wonder whether or not the nonvertebrate animals would feel pain. A few years ago they found endorphins, which are substances that handle chronic pain, in earth worms. So, earth wvrms may in fact be subject to chronic pain when you're putting them on that hook.***

Phil Donahue with John E. McArdle, Humane Society of the United States
Donahue (transcript #02065)
February 1985

Although the highest standard of protection must be applied to all animals, we acknowledge that it is right to pay special attention to the companions of man [non-human primates, cats, dogs, and equidae] for whom there is the greatest public concern.

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This report assesses the state of the art and the potential for alternatives to using animals in three contexts: biomedical and behavioral research, testing of products for toxicity, and education. Distinguishing among these three areas is important because both the patterns of animal use and the potential for alternatives vary among them. Research develops new knowledge and new technologies; although prediction of results is one goal, unpredictable results may prove even more significant. Testing relies on standardized procedures that have been demonstrated to predict certain health effects in humans or animals. It entails the measurement of biological phenomena, such as the presence or absence of cancer or of skin irritation, or the concentration of certain substances in tissue or in bodily fluids. Education involves teaching students in the life sciences, health professionals and preprofessionals, and research scientists, as well as the cultivation of humane attitudes toward animals at all levels. Alternatives in each of these three areas consist of procedures that replace animals with nonanimal methods, that reduce the number of animals used, or that refine existing protocols to make them more humane.

In addition to evaluating alternatives in three areas, the assessment also examines ethical concerns regarding the use of animals, economic considerations of their use and the alternatives, funding for the development of alternatives, and current regulation of animal use, Most important, this report delineates seven major public policy issues (and associated options for congressional action) in relation to alternatives (see ch. 1).

With a focus on the prospects for alternatives to animal use in research, testing, and education, this assessment necessarily excludes certain related topics and treats others only in brief. The role of animals in food and fiber production falls outside the scope of this study, as does the role of animals in the commercial production of antibodies and other biological materials. In addition, OTA has not evaluated the use of animals for companionship, sport, or entertainment. Although laboratory animals are an integral part of this assessment, OTA did not examine contemporary standards of their care (e.g., cage size, sanitation, ventilation, feeding, and watering). Lastly, the use of human subjects is not considered in this assessment.

WHAT IS AN ANIMAL?

In any biological definition of the word "animal," all vertebrate and invertebrate organisms are ineluded and plants and unicellular organisms are excluded. For the purposes of this report, however, **an "animal" is defined as any member of the five classes of vertebrates (nonhuman mammals, birds, reptiles, amphibians, and fish).** These five classes of vertebrates can be further divided into two major groups, cold-blooded vertebrates (reptiles, amphibians, and fish) and warm-blooded vertebrates (mammals and birds). Invertebrates, therefore, are not discussed as animals.

Political and scientific discussions often incorporate other subdivisions for the term "animal." Although not strictly part of the definition in this report, the terms "lower" and '(higher" are used in many discussions of alternatives that refine existing animal procedures or that replace certain animal species with other ones. In these contexts, the substitution of "lower" animals for '(higher" animals usually refers to using cold-blooded vertebrates instead of warm-blooded vertebrates. In addition, within the class of mammals, "lower" is generally used to designate, for example, rodents, while "higher" refers to primates, companion animal species (e.g., dogs, cats, or rabbits), and domestic farm animals (e.g., horses, cattle, or pigs).

Table 2-1 is a classification of the principal living organisms that are used in research, testing, and education. It indicates the laboratory species falling within this assessment's definition of an animal and the species that can be classified as "alternatives."

Table 2.1.—Some Types of Living Organisms Used in Research, Testing, and Education

Alternatives:

1. Prokaryotes (any living organism without a nuclear membrane)
- A. Bacteria
  - 1. *Escherichia coli*
  - *2. Salmonella*
  - *3. Streptococcus*
  - *4. Bacillus*
- B. Fungi—e.g., yeast

II. Eukaryotes (any living organism with a nuclear membrane)
- A. Plants
- B. Invertebrates
  - 1. Protozoa
    - a. *Paramecium*
    - b. *Amoeba*
  - *2.* Porifera—e.g., sponges
  - 3. Coelenterates—e. g., ***Hydra*** and Jellyfish
  - 4. Flatworms—e.g., *Planaria*
  - *5.* Segmented worms
    - a. Earthworms
    - b. Leeches
    - c. Annelids
  - 6. Nematodes—e.g., Caenorhabdiitis elegans
  - 7. Molluscs
    - a. Gastropods—e.g., snails and *Aplysia*
    - b. Pelecypods—e.g., mussels
    - c. Cephalopods—e.g., squids and octopuses
  - 8. Arthropods
    - a. *Lirnulus* (horseshoe crabs)
    - b. Arachnids
      - (1) Spiders
      - (2) Ticks
      - (3) Mites
      - (4) Scorpions
    - c. Crustaceans
      - (1) *Daphnia*
      - *(2)* Brine shrimp
      - (3) Crayfish
    - d. Insects
      - (1) Crickets
      - (2) Cockroaches
      - (3) *Drosophila* (fruit flies)
      - (4) Lice
      - (5) Beetles
      - (6) Moths
      - (7) Butterflies
  - 9. Echinoderms
    - a. Sea urchins
    - b. Sand dollars
    - c. Sea cucumbers

Animals:

- **C.** Vertebrates
  - 1. Cold-blooded vertebrates
    - a. Fish
      - (1) Jawless fish–e.g., lampreys
      - (2) Cartilaginous fish–e.g., sharks
      - (3) Bony fish
    - b. Amphibians
      - (1) Frogs—e.g., *Rana*
      - *(2)* Toads–e.g., *Xenopus*
      - (3) Salamanders
    - c. Reptiles
      - (1) Turtles
      - (2) Crocodiles
      - (3) Alligators
      - (4) Snakes
      - (5) Lizards
  - 2. Warm-blooded vertebrates
    - a. Birds
      - (1) Quail
      - (2) Chickens
      - (3) Pigeons
      - (4) Doves
      - (5) Ducks
    - b. Mammals
      - (1) Bats
      - (2) Rodents
        - (a) Mice
        - (b) Rats
        - (c) Gerbils
        - (d) Guinea pigs
        - (e) Hamsters
        - (f) Squirrels
      - (3) Marine mammals
        - (a) Dolphins
        - (b) Whales
        - (c) Seals
        - (d) Sea lions
      - (4) Rabbits
      - (5) Armadillos
      - (6) Carnivores
        - (a) Dogs
        - (b) Cats
        - (c) Ferrets
      - (7) Ungulates
        - (a) Cattle
        - (b) Sheep
        - (c) Horses
        - (d) Pigs
        - (e) Miniature pigs
        - (f) Goats
        - (g) Donkeys
        - (h) Burros
      - (8) Primates
        - (a) Baboons
        - (b) Capuchins
        - (c) Chimpanzees
        - (d) Macaques, Cynomolgous
        - (e) Macaques, Pig-tailed
        - (f) Macaques, Rhesus
        - (g) Marmosets
        - (h) Squirrel monkeys

SOURCE: Off Ice of Technology Assessment.

WHAT IS AN ALTERNATIVE?

Defining the word "alternative" is in a sense always doomed to failure: Regardless of how accommodating or strict the definition, many will fault it. The term evolved in the political arena, coined by animal welfare activists and for the most part nonscientists, and yet it has direct implications for scientists using laboratory animals. Its meaning varies greatly, depending on who uses it and the context in which it is used.

The definition of "alternatives" employed by OTA obviously affects this entire assessment: It defines the scope of the study. Too narrow a definition would dispose of the need for this report, while too broad a definition would render it unmanageable. Defining alternatives as the nonuse of animals, as some would have it, would restrict the bounds of the study to the consideration of invertebrate organisms, chemicals, plants, and computers. On the other hand, stretching the definition to include humans, for example, would create a whole new series of issues that would be virtually impossible to address within one assessment. With these concerns in mind, **OTA chose to define "alternatives" as encompassing any subjects, protocols, or technologies that '(*replace* the use of laboratory animals altogether, reduce the number of animals required, or *refine* existing procedures or techniques so as to minimize the level of stress endured by the animal" (4;** adapted from 5).

Some examples of alternatives under this definition include computer simulations to demonstrate principles of physiology to medical students, the use of the approximate lethal dose methodology in acute toxicity studies, and the increased use of anesthetics with pain research subjects. The "reduction" part of the definition indicates that the increased use of cultured cells, tissues, and organs instead of whole animals is also an alternative. A very broad interpretation of alternatives might also include the substitution of cold-blooded for warm-blooded vertebrates.

BIOLOGICAL MODELS

When animals-or alternatives—are used in research, testing, and education, it is because they possess a simpler or more accessible structure or mechanism in comparison with the object of primary interest (which is often the human) or are themselves the object of primary interest, or because certain procedures cannot be carried out on humans. Viewed from this perspective, both animals and alternatives stand as models. In the broadest sense, a biological model is a surrogate, or substitute, for any processor organism of ultimate interest to the investigator. It is a representation of or analog to some living structure, organism, or process.

In addition to analogy, biology has another analytical tool at its disposal—homology, which is correspondence in structure and function derived from a common evolutionary origin (i.e., a common gene sequence). The most closely related species are generally presumed to offer the best homologs. Relationships between species are not always known in detail, however, and unresolved questions about evolutionary events and pathways are numerous. Care must therefore be used in evaluating the degree of homology and the extent to which it relates to analogy ***(3).***

Some biological mechanisms, such as the coding of genetic information and the pathways of metabolism, arose early in evolution. These mechanisms have been highly conserved and are widely shared by organisms, including humans, at the cellular and molecular levels. Thus, good models for these fundamental molecular mechanisms in humans can be found in a wide array of organisms, some of which, such as bacteria, have structures and functions far less complex than those of mammals (3).

Several characteristics are important in choosing a model for research, testing, or educational purposes. The most important is the model's discrimination-the extent to which it reproduces the particular property in which the investigator is interested. With greater discrimination, the predictability between the model and the property under study increases.

After the discrimination or predictability of a model, certain other criteria stand out as being necessary for a good biological model (1)2). A model should:

- accurately reproduce the disease or lesion under study;
- be available to multiple investigators;
- be exportable from one laboratory to another;
- be large enough to yield multiple samples;
- fit into available facilities of most laboratories;
- be capable of being handled by most investigators;
- survive long enough to be usable;
- exhibit the phenomenon under study with relative frequency;
- be of defined genetic homogeneity or heterogeneity;
- possess unique anatomical, physiological, or behavioral attributes;
- be accompanied by readily available background data; and
- be amenable to investigation with available, sophisticated techniques.

Depending on the type and needs of the investigation, certain of these criteria might be more important than others. Overall, a model with more of these characteristics will have higher discrimination and stronger predictive ability,

In research, testing, and education, a small number of species have achieved prominence as experimental tools because they have been extensively studied from a number of perspectives and thus provide well-understood paradigms that have been described in detail in terms of genetics, biochemistry, physiology, and other aspects. These organisms include the laboratory rat, laboratory mouse, fruit fly, and bacterium Escherichia coli. Yet taxonomic breadth is also required in research and testing, since it is often impossible to predict what species will lend themselves particularly well to the study of specific problems. In biological modeling, concentration on selected species and taxonomic diversity are not mutually exclusive; both play a role in the establishment of a maximally useful matrix of biological knowledge (3).

CHAPTER 2 REFERENCES

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