

Chapter 6

Patenting of Animals—Scientific and Regulatory Considerations

“The real issue is not whether animals can or should be patented, but what things it is reasonable to permit humans to do to animals. Patenting simply adds another incentive to profit-making organizations to pursue certain lines of animal experimentation, and makes this pursuit seem more legitimate.”

George Annas
Hastings Center Report, August 1987

“I think a lot of people believe there is a moral imperative to fight disease and hunger. Patenting animals is consistent with and furthers this imperative.”

Geoff Kamy
Patent Attorney, Vienna, VA

“The best way to predict the future is to invent it.”

John Sculley
Chairman, Apple computers,
Odyssey: Pepsi to Apple

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Patenting of Animals— Scientific and Regulatory Considerations

INTRODUCTION

The U.S. Patent and Trademark Office (PTO) Board of Appeals and Interferences, relying on precedent opinions by the Supreme Court and PTO Board of Appeals (5,8) in 1987 held that claimed polyploid oysters were patentable subject matter (7). Subsequent to this decision, PTO issued a policy statement announcing that it considered “nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter” (box 6-A).

Considerations of the patentability of human-engineered animals have raised a variety of issues. These include questions about the economic implications of allowing or not allowing animals to be

patented; the Federal regulatory apparatus with respect to transgenic animals; and ethical questions relevant to the patenting of animals. Ethical questions are examined in chapter 8. Some economic implications are outlined in chapter 7. Regulatory issues are explored below, following an introduction to some of the relevant scientific and technical background.

MODERN TECHNIQUES FOR PRODUCING TRANSGENIC ANIMALS

Most potentially patentable animals are likely to be transgenic animals produced via recombinant DNA (deoxyribonucleic acid) technique or genetic

Box 6-A—PTO Policy on Patenting of Animals

A decision by the Board of Appeals and Patent Interferences in *Ex parte Allen* (Bd. App. & Int. April 3, 1987) held that claimed polyploid oysters are nonnaturally occurring manufacture or compositions of matter within the meaning of 35 U.S.C. 101. The Board relied upon the opinion of the Supreme Court in *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980) as it had done in *Ex parte Hibberd*, 227 USPQ 443 (Bd. App. & Int. 1985), as controlling authority that the Congress intended statutory subject matter to “include anything under the sun that is made by man.” The Patent and Trademark Office now considers nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101.

The Board’s decision does not affect the principle and practice that products found in nature will not be considered to be patentable subject matter under 35 U.S.C. 101 and/or 102. An article of manufacture or composition of matter occurring in nature will not be considered patentable unless given a new form, quality, properties, or combination not present in the original article existing in nature in accordance with existing law. See e.g., *Funk Bros., Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 76 USPQ 280 (1948); *American Fruit Growers v. Brogdex*, 283 U.S. 1, 8 USPQ 131 (1931); *Ex parte Grayson*, 51 USPQ 413 (Bd. App. 1941).

A claim directed to or including within its scope a human being will not be considered to be patentable subject matter under 35 U.S.C. 101. The grant of a limited, but exclusive property right in a human being is prohibited by the Constitution. Accordingly, it is suggested that any claim directed to a nonplant multicellular organism which would include a human being within its scope include the limitation “nonhuman” to avoid this ground of rejection. The use of a negative limitation to define the metes and bounds of the claimed subject matter is a permissible form of expression. In *re Wakefield*, 422 F.2d 897, 164 USPQ 636 (CCPA 1970).

Accordingly, the Patent and Trademark Office is now examining claims directed to multicellular living organisms, including animals. To the extent that the claimed subject matter is directed to a nonhuman “nonnaturally occurring manufacture or composition of matter—a product of human ingenuity” (*Diamond v. Chakrabarty*), such claims will not be rejected under 35 U.S.C. 101 as being directed to nonstatutory subject matter.

Date: 4-7-87
s/ Donald J. Quigg
Assistant Secretary and Commissioner
of Patents and Trademarks

SOURCE: U.S. Patent and Trademark Office, 1987.

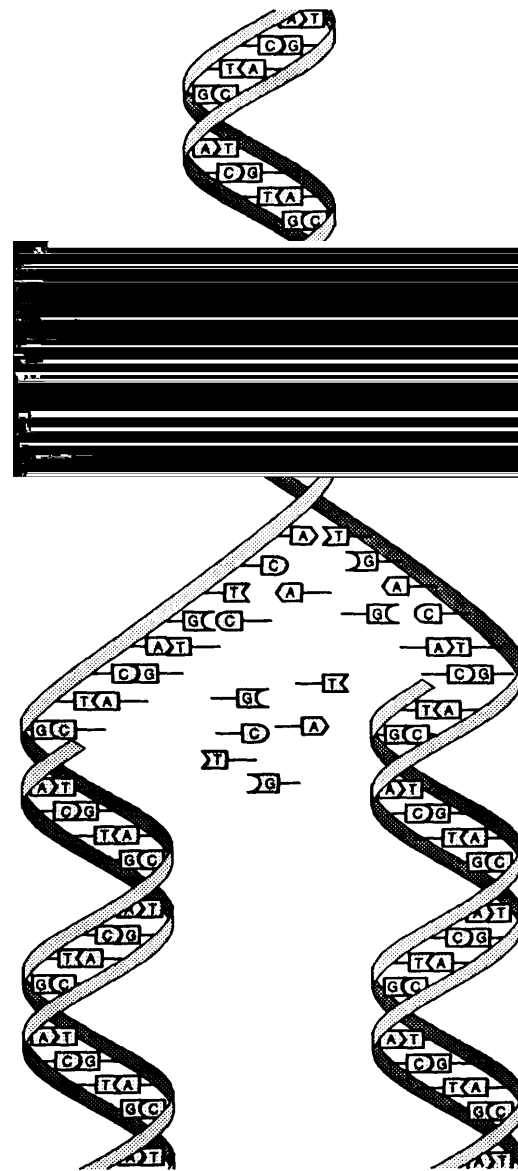
engineering. Transgenic animals are those to whose DNA, or hereditary material, has been added DNA from a source other than parental germplasm, usually from different animals or from humans. The following section describes the most common of the new techniques researchers use to move genes between animals, and compares them with historical breeding practices in animal breeding and husbandry. It also looks ahead to predict potential applications of these new techniques.

Laboratories around the world are conducting substantial research that involves inserting genes from vertebrates (including humans and other mammals) into bacteria, yeast, insect viruses, or mammalian cells in culture. This research is aimed primarily at increasing understanding of the organization and function of the hereditary material, DNA (figure 6-1). DNA, packaged in genes, encodes information that directs the construction and regulates the function of all higher organisms. DNA accomplishes this by modulating the enormous variety of biochemical activities in living cells. Understanding has advanced to the level that some bacteria, yeast, or cell cultures can now be used as factories for the production of high-quality pharmaceuticals such as human insulin, interferon, or growth hormone for use in the treatment of human disease or for other purposes. The equipment and personnel training requirements for such work are, as scientific research goes, modest.

A variety of techniques, most developed from early bacterial research, can now be used to insert genes from one animal into another. These techniques are known by a number of exotic names: microinjection, cell fusion, electroporation, retroviral transformation, and others. This section focuses largely on microinjection, because it is now the method most commonly used and most likely to lead to practical applications in mammals. Other methods of gene insertion may become more widely used in the future as techniques are refined and improved. If protocols for human gene therapy now being developed in animal models or laboratory cultures of mammalian cells prove successful and broadly adaptable to other mammals, other gene insertion techniques may well supplant microinjection.

In the early 1980s, researchers developed techniques for producing transgenic animals to the

Figure 6-1—Replication of DNA



When DNA replicates, the original strands unwind and serve as templates for the building of new, complementary strands. The daughter molecules are exact copies of the parent, each daughter having one of the parent strands.

SOURCE: Office of Technology Assessment, 1989.

extent that they could be applied successfully with properly trained and skilled staff and about \$50,000 worth of equipment (2,24). Rearing and maintenance facilities for the most commonly used research organism, the mouse, cost between \$10,000 and \$100,000 annually (3) (table 6-1). Comparable

Table 6-1—Advantages of Mice for Research in Gene Transplantation

- . A warm-blooded mammal with many similarities to humans in genetics and physiology.
- . Small organism, easy to maintain in the lab, can be raised in substantial numbers easily and quickly, at modest expense.
- . Compared to other mammals, genetics and physiology very well known.
- . Available in a variety of different, well-characterized, genetically consistent lines for use in different types of studies.

SOURCE: Office of Technology Assessment, 1989.

facilities for larger organisms (e.g., swine, cattle) are more expensive.

Although the number of laboratories working with transgenic animals remains small (no more than a few hundred, worldwide) and researchers with the required skill and experience are not common, the number of research programs using these techniques has grown steadily in recent years (3). For reasons of convenience, much research involving transgenic mammals continues to be done using mice (table 6-1), although research programs on several larger mammals have made significant progress. It is anticipated that some animals of research utility or substantial economic importance will become more common as subjects of transgenic modifications in the near future (within 5 to 10 years). Beyond mice, the major research efforts involving transgenic modifications focus on cattle, swine, sheep, poultry, and fish.

Gene Insertion Into Bacteria

Procedures to produce transgenic organisms (those that have integrated DNA from foreign sources) were first developed in bacteria (28). The techniques for introducing a foreign gene into a bacterium and achieving normal expression and function are fairly simple. Certain bacterial enzymes, known as restriction enzymes, recognize specific, short sequences of DNA (ranging from 4 to 12 nucleotide base pairs in length) and cut the DNA molecule where these sites occur. Using these restriction enzymes (over 400 are known, capable of cutting DNA molecules at over 100 different recognition sequences) it is possible to extract an entire gene that has been identified in the hereditary material of an organism. This gene can be linked with a DNA molecule, called a vector, which

is then inserted into a bacterium. The vector can exist in the bacterial cell, carrying along with it the inserted gene (figure 6-2). It is by this method that a gene coding for the production of human insulin, for example, can be excised from human DNA and inserted into the bacterium *Escherichia coli*. The altered bacterium then produces quantities of human insulin that can be extracted and administered to human diabetics to help treat their disease.

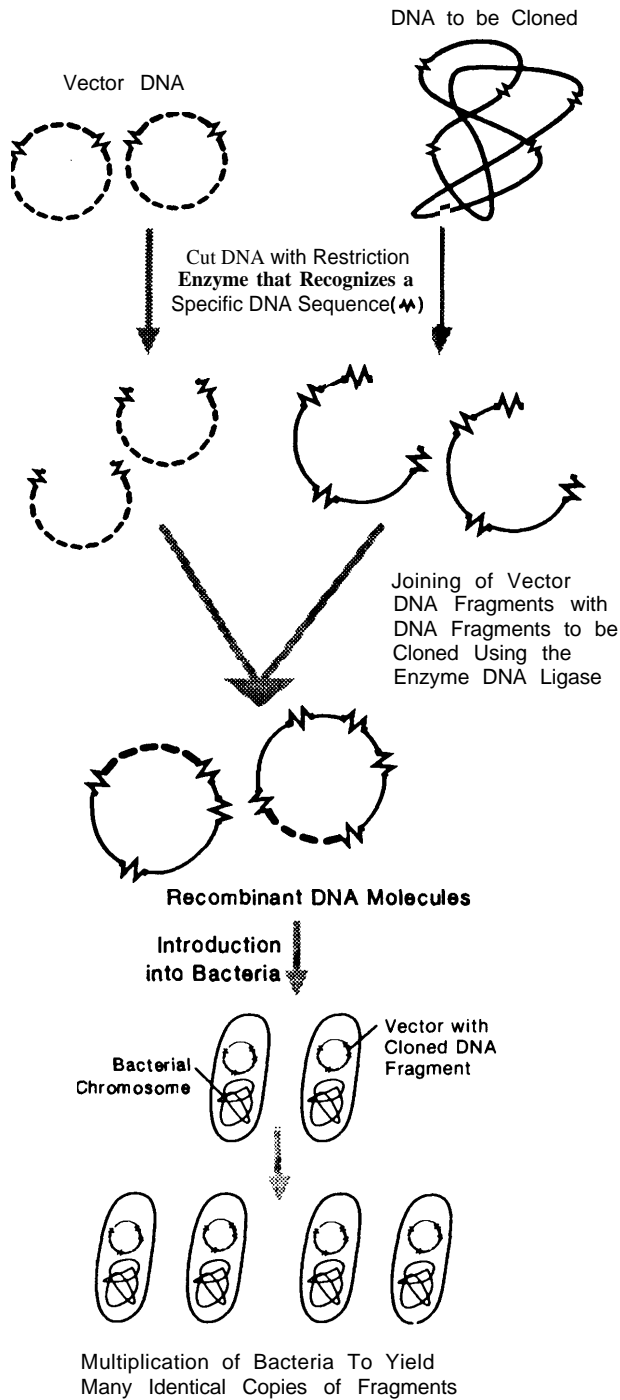
Gene Insertion Into Animals: Microinjection

Inserting a gene from one animal into the cells of another animal (as opposed to a bacterium) is more complicated and, at present, less precise. One of the ways in which animals differ from bacteria is that animal cells generally do not contain free floating, independently replicating DNA particles, or plasmids, of the type that can be used to transport genetic material between different cells. To compensate for this lack of a convenient delivery vehicle, researchers most commonly will inject highly purified copies of the gene of interest directly into the fertilized animal egg. Shortly thereafter, the fertilized egg is surgically implanted in a female's reproductive tract. This injection process is quite delicate, and only a small fraction of injected eggs (perhaps 1 to 5 percent) develop into transgenic animals (figure 6-3).

In experiments with mice, the fertilized eggs are placed under a special microscope, positioned, and held in place by a special glass tube that can be moved with a micromanipulator (a sensitive set of mechanical manipulators). Another glass tube with a smaller tip is then used to penetrate through the egg membrane into the pronucleus, the cellular subunit within which will develop the nucleus. The penetrating tube carries a small amount of a buffer solution that delivers numerous highly purified copies of the gene of interest (figure 6-4). The injected eggs are then placed back into the appropriate location in the reproductive tract of a receptive female mouse, which gestates the eggs and brings them to term.

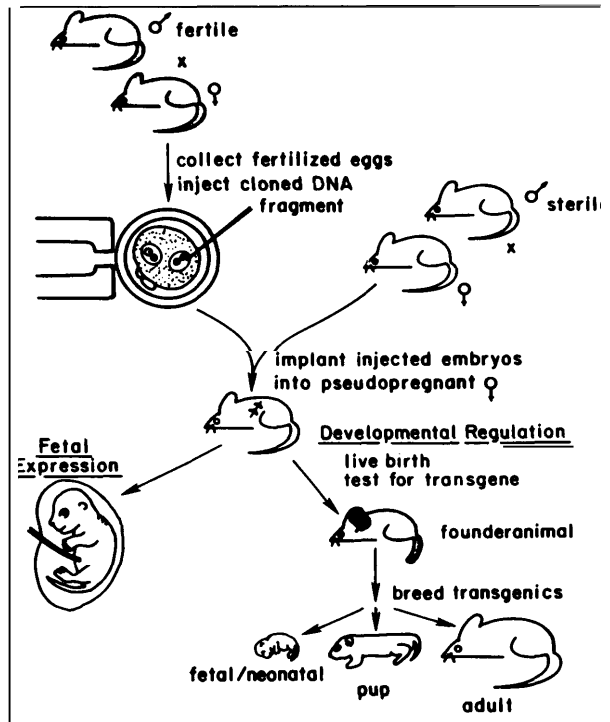
Overall, microinjection is tedious, labor intensive, and inefficient. Aside from the problems inherent in any system that must rely on delicate and sensitive micromanipulations, additional disadvantages stem from the current lack of knowledge concerning how to direct inserted DNA to a particu-

Figure 6-2-DNA Cloning With Vectors



SOURCE: Office of Technology Assessment, 1989.

Figure 6-3-Process of Producing a Transgenic Mouse



Fertilized eggs are collected, injected with cloned DNA, and transferred to a pseudopregnant foster mother. Two strategies are generally taken in analyzing transgenic mice. If the response of the transgene to environmental stimuli or developmental regulation is to be examined, it is best to establish a transgenic line of mice.

SOURCE: Sally A. Camper, Fox Chase Cancer Center.

lar or appropriate site for integration into the new host chromosome. In an accomplished laboratory, of every 100 eggs that are collected perhaps 85 percent of them prove suitable for injection; of these injected eggs, about 60 survive the injection procedure; 6 of the injected eggs that are returned to the host mother result in live births, and 1 or 2 will produce transgenic mice (3). This is the method that was used to introduce the gene encoding human growth hormone into mice, resulting in larger-than-usual mice (2). It is also the method used to produce mice that secrete the anti-clotting agent tissue plasminogen activator (tPA) in their milk (11).

As crude and tedious as this process is, it compares favorably in at least three respects with those techniques for producing comparable animals that have long been used (e.g., selective breeding):

Figure 6-4--Microinjection of Gene Into a Mouse Cell

The egg is held on the right by a holding pipet under suction, and the needle containing the DNA solution is positioned at the left (upper panel). A successful injection results in the obvious swelling of the pronucleus; compare lower panel with the upper panel.

SOURCE R.L. Brinster and M.E. Trubauer, University of Pennsylvania, School of Veterinary Medicine.

- The rapidity with which a specific gene can be inserted into a desired host means that **the time it takes to establish a line of animals carrying (and expressing) the desired trait is much reduced.** It is theoretically possible to produce a line carrying the desired trait after as little as one generation. In contrast, it takes many generations of selective breeding to establish a desired trait (usually a polygenic trait, one controlled by several genes) in a line with a minimum of additional, unwanted characteristics—something that was not always possible.

- The specific gene of interest can be transferred with great confidence, if not efficiency, and if proper purification protocols are followed, **without any accompanying, unwanted genetic material.** With the breeding methods that animal breeders have been using for centuries, the transfer of the desired gene (which was not even recognized as a gene, or a discrete hereditary unit, until 1900) was often accompanied by the simultaneous transfer of large amounts of additional genetic material which often complicated or confounded the objectives of the breeding programs as extraneous varying factors were introduced (e.g., changes in temperament or disease resistance).
- With the proper preparation, genes from almost any organism can be inserted into the desired host, whether it is a mouse or some other animal. Historically, genetic material exchanged by classical hybridization (crossbreeding) could only be transferred between closely related species or different strains within a species.

Where These Techniques Are Likely to Lead

Previous methods of gene transfer have been used for thousands of years to alter animals, plants, and microbes to serve human purposes (25). Many feel the new techniques involve no radical, qualitative departure from historical practices but simply enable plant and animal breeders to do the same things they have always done, but more quickly, easily, and predictably (22). If there is a fundamental difference brought by the new techniques, it is that breeders have a greatly augmented ability to move genes between organisms that are not close genetic relatives (e.g., human and mouse or human and bacterium). Generally it would have been impossible to make these gene transfers with the methods previously available. But most students of species and species formation are in general agreement that nothing in transgenic animal research or its potential commercial applications brings any significant threats to species; such threats, rather, are more easily found in patterns of land use planning or habitat destruction resulting from other human activities.

It is reasonable to expect that transgenic techniques will be used in much the same way historical

techniques have been used, to similar ends. Economic considerations will have the major influence on the order in which different transgenic animals are produced for commercial use. **Transgenic animals designed for biomedical research are likely to be patented first. Although transgenic agricultural animals such as livestock and poultry can be expected to be produced in the near future, the view most widely held among researchers is that it may be 10 years or more before commercial herds or flocks of transgenic livestock are produced.** Under optimistic assumptions, production may be possible within 3 to 4 years, though few scientists regard this scenario as likely.

The first animal actually patented was a mouse engineered by researchers at Harvard University for use in studies of carcinogenicity (box 6-B). Most transgenic animal research in the near future will likely focus on traits involving a single gene, often with associated control sequences. Already single genes have been introduced into animals allowing them to produce substances they previously could not. Other examples of potentially patentable transgenic animals include the mouse that produces tPA and the introduction of the human growth hormone gene into mice and pigs producing larger, leaner animals. Genes might also be introduced into an animal to give it the ability to resist disease or parasites. However, manipulation of complex traits influenced by more than one gene such as the amount of growth possible on a limited food regimen or behavioral characteristics, will develop more slowly (perhaps within 10 to 30 years) because of greater technical difficulty and current lack of understanding about how such traits are controlled by genes. It is reasonable to suppose that smaller markets, such as domestic pets, will also see applications of the new techniques as they become more efficient and economical.

Much transgenic animal research is aimed at increasing understanding of human diseases and therefore involves the insertion of genes from humans into other organisms. **Much research not aimed at human disease also involves the insertion of human genes into animals. The principal reason for this is convenience: the growing amount of research aimed at identifying, extracting, and characterizing human genes means that**

they will become more common and available. The range of genetic variation within any species and the fundamental similarity in genetic structure and organization between all mammals often make it impossible to tell, simply from looking at an isolated gene or nucleotide sequence, what species it was derived from. Lacking any essential, identifying link between a gene and the organism that carries it, the convenience of using the most readily available genetic material will be the decisive factor in selecting genes for insertion into other organisms.

It is unlikely that genes from animals will be introduced into humans in the near future, for reasons of biology if not of ethics, psychology, or aesthetics. Society is approaching somatic cell human gene therapy with considerable caution even when it involves the transfer of human genes (26). In the absence of any compelling biological reasons (which have not yet emerged) it does not appear that any researchers are presently planning to insert into humans, genes originating in other animals. Advances in DNA chemistry and protein engineering may ultimately make some (but not all) such questions moot, as the ability to entirely synthesize genes that would direct the construction of specific gene products advances.

Species and Transgenic Animals

Some concern has been raised over negative impacts transgenic animals might have on their own species. At least one opponent of animal patents has asserted that transferring genes between species transgresses natural barriers between species, violating their integrity or their identity (23). To evaluate the quality or magnitude of such an alleged danger, it is useful to consider historical notions of species identity and what biologists now feel it means for an individual organism to belong to a given species.

Before Darwin, a species was conceived of as a static, unitary group or type of organism. Individuals belonging to such a group were so classified because they were felt to embody or reflect certain essential or ideal characteristics. This definition of species was first systematically applied to living things by the Swedish biologist Carolus Linnaeus (1707-1778). Such an approach has clear roots in Platonic philosophy, however, which can be traced directly to

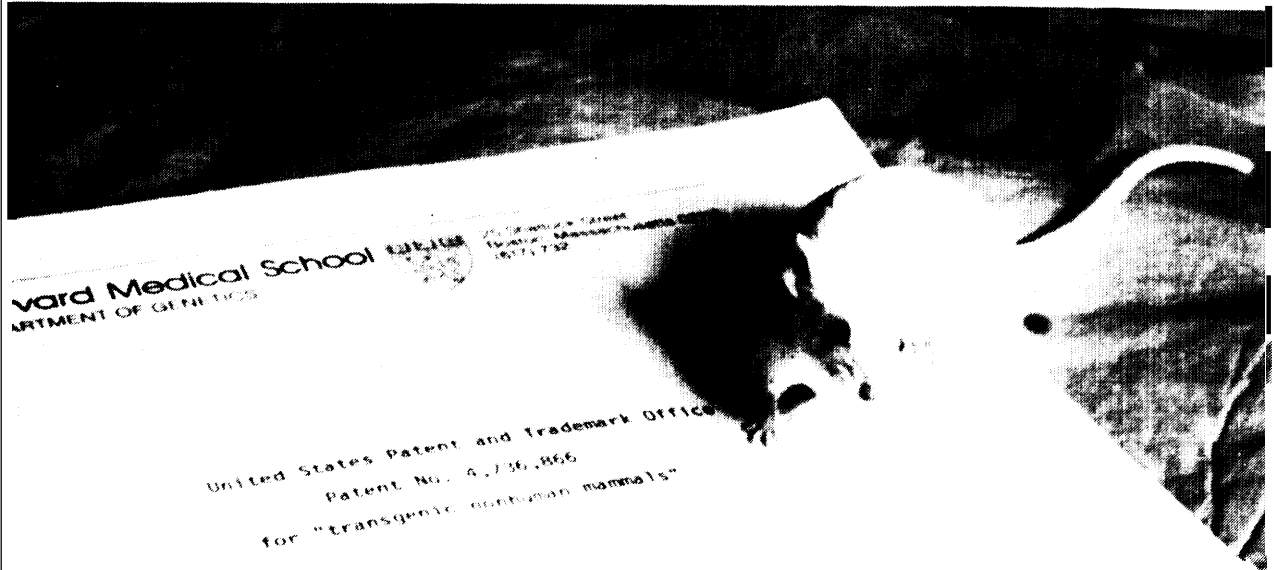
Box 6-B—Patent Number 4,736,866—The “Harvard Mouse”

Photo credit: Ira Wyman/Sigma

On April 12, 1988, the U.S. Patent Office issued the first patent of a living animal to Harvard Professor Philip Leder and Timothy A. Stewart of San Francisco, California. The patent was assigned to the President and Fellows of Harvard College. The patent claims “a transgenic nonhuman eukaryotic animal (preferably a rodent such as a mouse) whose germ cells and somatic cells contain an activated oncogene sequence.” The claim cited a mouse into which had been inserted a gene that causes an increased propensity for the mouse to develop cancerous tumors. Such mice can be used to test materials suspected of being carcinogens. These tests “can be extremely sensitive” and “will permit suspect materials to be tested in much smaller amounts than . . . used in current animal carcinogenicity studies.” The patent points out that this “will minimize one source of criticism of current (testing) methods, that their validity is questionable because the amounts of the tested material used is greatly in excess of amounts to which humans are likely to be exposed.”

Such transgenic mice “can also be used as tester animals for materials . . . thought to confer protection against the development of” cancerous tumors (e.g., antioxidants such as beta-carotene or Vitamin E).

The precise language of the patent described several similar lines of laboratory mice that had been engineered by the insertion of an activated oncogene sequence, specifically, the mouse “myc” (myelocytomatosis) gene under control of a promoter or regulatory gene sequence derived from the mouse mammary tumor virus (MMTV LTR). Gene fusions of the myc and MMTV LTR genes were created and inserted into fertilized one-cell mouse eggs via micro-injection. The treated eggs were then implanted in receptive female mice and the offspring were raised, used to establish laboratory populations, and then analyzed for incorporation and expression of the inserted genes.

The actual patent coverage is broad, embracing virtually any species of “transgenic nonhuman mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage.”

SOURCE: U.S. Patent and Trademark Office, U.S. Patent No. 4,736,866 (1988).

the “Allegory of the Cave” developed in Plato’s *Republic* (13,19,21). Aristotle’s understanding of species was similar, and many aspects of philosophi-

cal and biological thought throughout the middle ages reflected this Platonic approach (17,20,21). Such thinking was increasingly felt to be inadequate



Photo credit: R.L. Brinster and R.E. Hammer, School of Veterinary Medicine, University of Pennsylvania

These female siblings are 24-week-old mice from a gene transfer experiment. The mouse on the right contains a new gene composed of the mouse metallothionein promoter/regulator fused to the human growth structural gene. The female with the gene weighs 59 grams and her sister without the gene weighs 28 grams.

and was challenged during the Renaissance. It was finally repudiated by Darwin in *The Origin of Species* in 1859.

Darwin introduced the idea of species as dynamic and necessarily transitory populations united by descent from a common ancestor but nonetheless comprising different individuals varying with respect to many different characteristics. In Darwin's time, however, there was not yet a science of genetics, nor was there any material understanding of the mechanisms of heredity. This made it impossible to understand the means by which species are formed or maintain continuity through time. Nonetheless, Darwin succeeded in changing the thinking of biologists about species from a perspective that was essentially Platonic, or topolog-

ical, to one that is population-based and considers variation within a population as integral to the nature of species rather than distracting and incidental.

Building upon this paradigmatic shift in biological thought, modern biologists now generally think of species as reproductive communities, **or populations. They are distinguished by their collective manifestation of ranges of variation with respect to many different characteristics or qualities simultaneously.** The parameters that delimit these ranges of variation are fluid and variable themselves: different species may have substantially different genetic population structures, and a given species may look significantly different in one part of its range than it does in another while still demonstrably belonging to the same gene pool, or reproductive

community (6). One species may exchange little or no genetic material with related or adjacent species, while another may seem to be almost promiscuous, interbreeding frequently with a neighboring, related species. Sometimes this gene flow (or introgression) produces peculiar populations that are different from either parent population and capable of interbreeding with one or both. In other cases, though genes may move more or less freely between species and genes from one species can be detected in individuals of another, biologists still have no difficulty in determining the species to which an individual belongs (9,19,29). Although research into the nature of species continues to be vigorous, marked by much discussion and disagreement among specialists, general agreement among biologists exists on at least one point: nature makes it clear that **there is no universal or absolute rule that all species are discretely bounded in any generally consistent manner.**

The issue of **species integrity** is more complex and subtle than that of **species barriers**. If a species can be thought of as having integrity as a biological unit, that integrity must, because of the nature of species, be rooted in the identity of the genetic material carried by the species. Precisely how a species might be defined genetically is not yet apparent. This issue is presently the subject of a great deal of intellectual excitement and ferment among those seeking to understand the nature of species. It is clear, however, that a genetic definition must embrace the possibility of a wide spectrum of variation in DNA sequence and organization simultaneously over many different portions of the genetic material of an organism (16). Any genetic definition of species must also embrace dramatic genetic mutations and malformations (19) that occur naturally. Individual examples of mutations are often unusual, but common in the aggregate, and not viewed as violating anything essential to the species in which they are found.

In short, any genetic definition of species grounded in the perception of a species as a dynamic population, rather than a unit, cannot be simple; it must be statistical and complex. Therefore, **to violate the “integrity” of a species it is not sufficient to find a particular gene, once widespread throughout the species, now entirely replaced by a different gene.** Such changes occur

repeatedly throughout the evolutionary history of a lineage and are described as microevolutionary. These changes are usually insufficient to alter a species in any fundamental way or to threaten any perceived genetic integrity. (27).

If it is possible to challenge the integrity of a species, it would have to be by changing or disrupting something fundamental in its genetic architecture, organization, or function. Mammals like mice, cattle, or humans may contain from 50,000 to 100,000 or more genes (4,9). Whatever it is in the organization and coordination of activity between these genes that is fundamental to their identity as species is not likely to be disrupted by the simple insertion or manipulation of small numbers of genes (fewer than 20) that transgenic animal research will involve for the foreseeable future. Any disruption of the genetic basis of species identity would most likely be accomplished by causing a fundamental change in the patterns of transmission by which hereditary information is passed from one generation to the next, e.g., impeding gene flow between populations that would otherwise commingle. Such a change in patterns must make it impossible, or at the very least difficult, for further genetic information to be transmitted between generations.

Changes in the patterns of transmission are known in some plants, insects, fish, and amphibians. They are much less easily accomplished in warm-blooded vertebrates, especially those likely to be subjects of transgenic research in the foreseeable future. In general, the biological characteristics crucial to such fundamental changes are most often controlled by several, or more likely many, genes distributed throughout the animal's genome and acting in a coordinated manner. Regulatory genes may often be involved, controlling the timing or levels of expression of one or more of the genes that specify the structure of a particular protein or enzyme (12,18). It is beyond the ability of current techniques to manipulate such characteristics with any significant precision.

In this context, it should also be observed that **“the right of a species to exist as a separate, identifiable creature” (23) has no known foundation in biology.** Species exist in nature as reproductive communities, not as separate creatures, and

these reproductive communities are, by standards of geologic time, temporary. The history of systematic and taxonomy (the disciplines of naming and describing species) demonstrates that species' existence has often been independent of scientists' shifting understanding or abilities to discern their existence. Furthermore, most of the domestic animals that are now the subjects of transgenic research (with the possible exception of some fish), and are likely to be for the foreseeable future, are already the products of centuries, and in many cases millennia, of human manipulation. Some observers think it reasonable to consider many domesticated animals as artificial species. Whatever integrity these species may once have had as biological units has already been far more compromised by human intervention than transgenic manipulations are likely to produce within the next decade or longer.

FEDERAL REGULATION AND ANIMAL PATENTS

To gain an understanding of the potential use and regulation of genetically altered animals that might be patented, OTA asked several Federal agencies' the following questions:

- How are genetically altered animals currently used in research, product development, and mission-oriented activities conducted or funded by your agency?
- What are the potential uses of such animals during the next 5 years?
- How does (or would) your agency regulate such animal use? What statutes, regulations, guidelines, or policy statements are relevant?

Eleven agencies responded to OTA's inquiry: the U.S. Patent and Trademark Office; the U.S. Department of Agriculture (Agricultural Research Service, Animal and Plant Health Inspection Service, Cooperative State Research Service, Food Safety and Inspection Service, and Office of Agricultural Biotechnology); the Food and Drug Administration; the Environmental Protection Agency; the National Science Foundation; the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health

Administration; the Agency for International Development; the Department of Interior (Fish and Wildlife Service); the National Aeronautics and Space Administration; and the Department of Energy (box 6-C).

U.S. Patent and Trademark Office

The Patent and Trademark Office (PTO), within the Department of Commerce, administers laws relating to the granting of patents for inventions. PTO examines applications; issues, records, and publishes patents that are granted; and maintains facilities for use by the public to examine issued patents and records. PTO has no jurisdiction over questions of infringement or enforcement of patents nor over matters relating to promotion or utilization of patents or inventions. PTO does not use genetically altered animals in any activity nor regulate the use of such animals. The agency is, however, responsible for determining whether to grant patents for such animals.

PTO anticipates an increase in the number of applications for genetically altered animals as a way of protecting inventions, since more people are likely to define their invention in terms of the ultimate product—the modified animal.

National Institutes of Health

Approximately half of the National Institutes of Health's (NIH's) research projects require the use of animals. There is no way to establish exactly how many of these research animals are genetically altered, but a significant proportion are thought to be so altered. Transgenic mice are used to study the basic biology of disease processes, including AIDS. The work focuses on analysis of how genes function in regulating cell specificity and the production of cellular products. In some cases, the potential exists for commercial drug production using transgenic animals.

Over the next 5 years, biomedical research will likely use transgenic animals in studies of diverse areas of abnormal development, birth defects, and chronic degenerative disease. Much work will center

¹OTA contacted Federal agencies listed as having regulatory responsibility under the Coordinated Framework for Regulation of Biotechnology (see *Federal Register*, June 26, 1986, page 23301 et seq.) or membership in the Interagency Research Animal Committee, a focal point for Federal agencies to discuss issues involving all animal species used in biomedical research and testing. A workshop on **Federal regulation** and animal patents was conducted by OTA on Dec. 11, 1987.

Box 6-C-Federal Statutes, Regulations, and Guidelines

Listed below is a synopsis of Federal statutes, regulations, and guidelines cited by Federal agencies at the OTA workshop of December 11, 1987.

Animal Welfare Act

Citation: 7 U.S.C. 2131-2155; 9 CFR 1-12.

Governs the transportation, sale, and handling of certain animals. As defined, an animal means any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, or rabbit.

Coordinated Framework for Regulation of Biotechnology

Citation: 51 FR 23301-23393

Notice issued by the Office of Science and Technology Policy describing Federal policies regulating the safety of biotechnology research and products. Policy statements were issued by the Food and Drug Administration, the Environmental Protection Agency, Department of Agriculture, Occupational Safety and Health Administration, and National Institutes of Health.

Endangered Species Act

Citation: 16 U.S.C. 1531-1543.

Could possibly apply if a Federal action potentially affected a species protected by the Act (see discussion under Fish and Wildlife section of text).

Federal Insecticide, Fungicide, and Rodenticide Act

Citation: 7 U.S.C. 136-136y.

FIFRA is a licensing statute under which EPA regulates the sale, distribution, and use of pesticides. Pursuant to this authority, EPA has routinely reviewed and registered micro-organisms for years.

Federal Meat Inspection Act

Citation: 21 U.S.C. 601-695; 9 CFR 301-381,

Poultry Products Inspection Act

Citation: 21 U.S.C. 451-470; 9 CFR Chapter 301-381.

These Acts require the Food Safety and Inspection Service to inspect cattle, sheep, swine, goats, equine, poultry, and food products prepared from them that are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled, marked, and inspected.

Food, Drug, and Cosmetics Act

Citation: 21 U.S.C. 301-392; 21 CFR 100-169 (regulations regarding food for human consumption).

Provides for regulatory oversight, approval, certification, and labeling of food, drugs and devices, and cosmetics.

Guide for the Care and Use of Laboratory Animals

Citation: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Publication No. 85-23, Bethesda, Md., Revised 1985.

Guide for the proper care and humane treatment of animals used in research. For purposes of the Guide, laboratory animals include any warm-blooded vertebrate animal used in research, testing, and education. The Guide deals with farm animals in the context of their use in biomedical research, not with their use in research on production agriculture.

Guidelines for Research Involving Recombinant DNA Molecules

Citation: 51 Fed. Reg. 16958, May 7, 1986 for most recent full version.

The Guidelines specify practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules. They are applicable to all recombinant DNA research within the United States or its territories which is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH. Any individual receiving support for research involving recombinant DNA must be associated with or sponsored by an institution that can and does assume the

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responsibilities assigned in the Guidelines. Recombinant DNA experiments involving whole animals or plants is covered under Section III-B-4.

Health Research Extension Act

Citation: Public Law 99-158

Amended the Public Health Service Act to provide for statutory authority for and recognition of the PHS Policy on *Humane Care and Use Of Laboratory Animals by Awardee Institutions*. The Act also contained provisions for the development of alternatives to animal use in research.

Public Health Service Policy on Humane Care and Use of Laboratory Animals

Citation: U.S. Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks, Bethesda, Md., Revised 1986.

Revised in 1986, this policy is used by all agencies of the Public Health Service and most Federal agencies to govern animal use. Unlike the Animal Welfare Act, the PHS policy applies to all vertebrate animals.

Lacey Act

Citation: 16 U.S.C. 701-718

Mandates the duties and powers of the Department of Interior to preserve migratory game and wild birds. Authority for Fish and Wildlife Service to enforce laws and regulations adopted by separate States.

Toxic Substances Control Act

Citation: 15 U.S.C. 2601-2654.

TSCA gives EPA jurisdiction over the manufacturing, processing, distribution, use, and disposal of all "chemical substances" in commerce or intended for entry into commerce that are not specifically covered by other regulatory authorities (e.g. foods, drugs, cosmetics, and pesticides). TSCA's applicability to regulating life forms that are products of biotechnology is based on the interpretation that living organisms are "chemical substances" **under the act** (i.e. "any organic. . . substance of a particular molecular identity, including. . . any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature . . ."). EPA does not anticipate regulating genetically engineered animals under TSCA.

U.S. Government Principles for the Care and Use of Vertebrate Animals Used in 'Ming, Research, and Training

Citation: 50 FR 20864 (1983)

A memorandum of understanding between APHIS, NIH, and FDA to exchange information on animal welfare concerns and compliance with policies.

Virus-Serum Toxin Act

Citation: 21 U.S.C. 151-157; 9 CFR 101-123.

APHIS would regulate the importation, interstate movement, and release into the environment of genetically altered animals when a biologic product (all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, and live micro-organisms; and the antigenic or immunizing components of micro-organisms intended for use in the diagnosis, treatment, or prevention of diseases of animals) is used.

SOURCE Office of Technology Assessment, 1989.

on manipulating DNA so that it can be expressed in specific organs. The targeted insertion of genes to repair defective chromosomes, which is not possible today, could become an important tool in combating disease in coming years. NIH researchers caution that the final characterization of animal models is a complex matter and is going to take time.

Authorities relied upon by NIH for the care and use of genetically altered animals include: the Animal Welfare Act; the Health Research Extension Act; the Guide for the Care and Use of Laboratory Animals; and the U.S. Government Principles for the Care and Use of Vertebrate Animals Used in Testing, Research, and Training.

The only policy specifically addressing use of genetically altered animals is **the NIH Guidelines for Research Involving Recombinant DNA Molecules**. According to NIH, the Guidelines for Research Involving Recombinant DNA Molecules apply more to the tools of the transgenic worker, such as bacterial cell lines, than to the animals themselves. The Guidelines specify practices for constructing and handling recombinant DNA molecules and organisms and viruses containing recombinant DNA molecules. The Guidelines apply to all recombinant DNA research within the United States or its territories that is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH. Any individual receiving support for research involving recombinant DNA must be associated with or sponsored by an institution that can and does assume the responsibilities assigned in the Guidelines. Recombinant DNA experiments involving whole animals are covered under Section III-B-4. The NIH Recombinant DNA Advisory Committee has approved additional guidelines to cover experimentation on transgenic animals. These establish containment guidelines for animals whose genome has been altered by the introduction of recombinant DNA into the germ line, as well as experiments involving viable recombinant DNA-modified micro-organisms tested on whole animals.

According to NIH, the Guidelines will likely apply to the majority of research involving transgenic animals as recombinant DNA techniques are usually used in such research. For example, recombinant DNA techniques are commonly used to produce cells that are often used in microinjection. The determining factor is whether recombinant DNA techniques are used during the experiment. The Guidelines would not apply, for example, in some instances where unaltered or “naked” DNA is microinjected (10).

The Guide for the Care and Use of Laboratory Animals addresses institutional policies, laboratory animal husbandry, veterinary care, and physical plant requirements for all NIH-funded research using warm-blooded vertebrate animals. The Guide, among other things, lists procedures for animal research involving hazardous agents.

In addition, NIH has animal care and use committees which are charged with reviewing all studies involving animals and recommending whether studies using animals should be performed. Researchers must submit a review of animal care and use for each study, including details about the facilities where the animals will be kept, to the NIH Office of Protection from Research Risks. A protocol or project can be referred to the NIH Biosafety Committee if further questions about safety are raised. An example of such a review involves a study in which genes from the human immunodeficiency virus will be introduced into mice.

All grantees must abide by NIH’s guidelines. The main sanction for violating the guidelines is suspension of funding. The American Association for Accreditation of Laboratory Animal Care also requires its members to follow the guidelines.

NIH has applied for patents stemming from past work, Interest in applying for patents has been stimulated by the passage of the Federal Technology Transfer Act (Public Law 96-502), which allows Federal laboratories to enter into cooperative research with private sector parties.

Alcohol, Drug Abuse, and Mental Health Administration

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) researchers mostly use human pedigree studies as a way to identify specific genes for associated diseases. In a few cases animal models have been used—for example in studying predispositions to alcohol consumption and drug abuse—but researchers have not yet isolated the genes that may be associated with those predispositions.

To date, ADAMHA researchers have not used transgenic animals. Within the next 5 years, however, research with transgenic animals is likely to be undertaken, particularly for research animal model use. Commercial products are not anticipated. ADAMHA grantees and researchers must follow the same regulations as those receiving NIH funds.

U.S. Department of Agriculture

The U.S. Department of Agriculture (USDA) is responsible for both enhancing and protecting American agriculture. It carries out these responsibilities through research and regulation. USDA has conducted research on the genetics of animals for many years. In addition to crossbreeding, genetic engineering provides a means to accelerate the rate at which researchers can improve the efficiency of animal production and the resistance of animals to disease.

The Agricultural Research Service (ARS) reported on two research projects involving genetically engineered animals. One entails studies of sheep and swine that have been altered by the addition of an extra growth hormone gene. The altered animals have been produced from fertilized eggs to which the gene has been added by microinjection. The objective of this work is to improve production characteristics such as growth rates and fat content of meat. The second project involves chickens engineered by recombinant DNA technology to be resistant to the avian leukosis virus, which causes a serious poultry disease.

In both cases, the genetic changes were permanent and transmittable to offspring. Avian leukosis resistance has been passed on through three descendant generations of chickens, demonstrating that the inserted gene has become a stable component of the



Photo credit: U.S. Department of Agriculture

Transgenic pig born at the USDA laboratory in Beltsville, MD.

chickens' hereditary material. The success of this type of work depends on the vector used to deliver the additional gene.

The efficiency of producing transgenic animals from the microinjection technique has so far been low—less than 1 percent in all experimental animals used. This illustrates that a considerable amount of work and technique is involved in developing an animal that is functionally transgenic.

In those animals expressing the new gene, the elevated level of growth hormone led to significant reductions in the amount of fat on the animal carcass. However, adverse effects on the animals have also been reported. The transgenic swine were more lethargic, arthritic, and susceptible to stress than standard breeds of domestic swine. According to ARS, more research is needed to learn how to overcome these drawbacks.

Barring unexpected breakthroughs, transgenic sheep and swine are not likely to become available for use in conventional livestock production systems within the next 10 years. Research on disease-resistant chickens could move faster, and genes of a harmless strain of avian leukosis virus could be in the parent poultry stock within 5 years. The same class of virus that causes avian leukosis occurs in other animals, so the technique used with chickens could conceivably be used to control other diseases in farm animals.

The Cooperative State Research Service (CSRS), which supports extramural research primarily at land grant universities and agricultural experimental stations, is in the early stages of developing genetically engineered animals. The work currently sponsored focuses on increasing knowledge about molecular structure, function, regulation, and expression of animal, microbial, and viral genes, with the goal of improving biological efficiency and disease resistance in domestic animals. Examples of research funded under the animal molecular biology program include: enhancement of disease resistance in genetically engineered swine, gene transfer to the germline of chickens using retroviral vectors, and gene transfer in fish.

Over the next **5 years**, research on genetically altered animals could increase knowledge about genetic maps of animals, specific genes of agricul-

tural importance, and tissue-specific and time-specific expression of genes in animals. This work, in turn, could be used to improve growth and feed efficiency, reproductive efficiency, and disease resistance.

The **Animal and Plant Health Inspection Service (APHIS)** is responsible for reviewing the genetic engineering techniques used before the altered animal is released from containment and for examining the capacity of the foreign genetic material in the host animal to cause disease. APHIS also exercises regulatory responsibilities related to the Animal Welfare Act which, among other provisions, requires protection of research animals. Although the Animal Welfare Act applies to all federally funded research, it applies to just six kinds of animals---cats, dogs, rabbits, hamsters, guinea pigs, and nonhuman primates-and excludes other rodents and farm animals.

APHIS' authority to regulate the importation, interstate movement, and release into the environment of genetically altered animals as biological products derives from the Virus-Serum-Toxin Act. By definition, a biological product includes antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases in animals (9 CFR 101.2(w)). The release from containment of genetically engineered animals is regulated under experimental production, distribution, and evaluation of biological products prior to licensing (9 CFR 103). If the means to produce a particular trait is not a biological product, as so defined, but is from a cell line or cell culture, APHIS could use its existing authority to regulate the introduction of such genetic material as an "organism" (9 CFR 122(e)). If the means used to produce the genetically altered animal is by introducing a retrovirus into the host animal, the altered animal could be regulated as a "vector" (9 CFR 122.1(f)).

APHIS is currently working with the Food and Drug Administration (FDA's) Center for Veterinary Medicine to develop a joint licensing and registration procedure for products that are classified as both a biologic and a drug.

Two other regulatory mechanisms are the Federal Meat Inspection Act and the Poultry Products Inspection Act, which require the USDA's **Food**

Safety and Inspection Service (FSIS) to inspect cattle, sheep, swine, goats, equines, poultry, and food products prepared from them that are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled (9 CFR 301-381).

One example of applying these regulations to genetically engineered animals is to see if the genetic transfer of one hormone stimulates the production of another hormone, such as estrogen. If so, the FDA, which is the primary agency responsible for regulating veterinary drugs, would be required to prescribe a withdrawal time for the genetically transferred hormone so that the meat of the animal did not contain the hormone when the animal was slaughtered. FSIS would determine, based on the evidence submitted, whether the meat was adulterated. FSIS also requires information to support a claim, for example, that an animal with a genetically transferred growth hormone has less fat.

Four categories of inspection exist for animal slaughter and inspection. Mandatory inspection is required for a number of species (cattle, sheep, swine, goats, equines, and poultry) under regulations mandated by the Federal Meat Inspection Act and the Poultry Products Inspection Act (9 CFR 301-335 and 9 CFR 381.1-381.311). The second classification, voluntary inspection, establishes a fee-for-service reimbursement program for the inspection of rabbits, domesticated reindeer, and buffalo (9 CFR 350,352,354). A third category, conditional inspection, is intended mainly for research or experimental animals (9 CFR 309.17 and 381.75). A fourth category covers custom processing of food animals (e.g., blends of game meat and inspected meat) that may be slaughtered for the sole use of the owner but may not be inspected or sold (9 CFR 303). These categories have been used to determine the method of inspection for so-called "cattalo" (resulting from direct crossbreeding of cattle and buffalo) and "beefalo" (a cross of three-eighths buffalo and five-eighths cattle). The precedent is a phenotypic criterion based on the physical appearance of the animal rather than on the genetic makeup (14). FSIS has proposed that legislation be considered to assure that lines of animals derived from genetically engineered animals are considered as belonging to the parent species.

To date, USDA does not have any patents pending for transgenic animals. However, applications for patents may be expected in the future.

Food and Drug Administration

FDA regulates food products for consumption, human and veterinary drugs, and medical devices (USDA regulates veterinary biologic). As primarily a regulatory agency, FDA is not involved in research with genetically engineered research animals.

The primary regulatory tools used by FDA are the Food, Drug, and Cosmetic Act and the Public Health Service Act. These laws cover human foods, veterinary drugs, the use of those drugs in food-producing animals, and human drugs and biological. The statutes apply to any product that is the result of a transgenic expression in an animal. According to FDA, this kind of regulation is an extension of what is currently done with more conventional technologies. As noted in the discussion of USDA research, if a drug is being used in a food animal, FDA regulations require that a certain withdrawal time be established before the animal can be slaughtered, to assure that the level of drug in the food chain does not exceed that which is safe for human consumption.

FDA has labeling authority for foods. The standard for labeling is to avoid anything that is false or misleading. Although the issue has not been formally raised, labels have been submitted where manufacturers wanted consumers to know that the food was a product of biotechnology. As for drugs and biological, recombinant insulin has been marketed without a specific notification that recombinant DNA technology was used to make it.

Responsibility for regulating food additives also falls under FDA's jurisdiction. Additives may not be included in a food product unless they are generally recognized as safe, or a petition for their use has been reviewed and approved by FDA. If a GRAS food substance is produced using a biotechnology process, in contrast to conventional methods, FDA would review it to ensure that the additive is still classified as GRAS, and that no new constituents have been added during the process.

Environmental Protection Agency

Genetically engineered animals are not currently used in any of the activities conducted or funded by the Environmental Protection Agency (EPA). It is not clear whether the patentability of animals would have any impact on EPA's work. EPA-funded research is now carried out only on micro-organisms, but it is conceivable that the agency eventually would fund research on macro-organisms, including animals.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) are the two statutes EPA uses to regulate biotechnology products.

Under FIFRA, the sale, distribution, and use of pesticides can be approved by EPA only if the pesticide will not cause "unreasonable" adverse effects to humans or the environment. Under this authority, EPA has routinely reviewed and registered micro-organisms.

TSCA gives EPA jurisdiction over the manufacturing, processing, distribution, use, and disposal of all chemical substances in commerce, or intended for commerce, that are not specifically covered by other regulatory agencies. These include foods, drugs, cosmetics, and pesticides. EPA has taken the position that living organisms are "chemical substances" under the Act. EPA's current regulatory policy for TSCA is directed to the review of micro-organisms. At this time, it is not EPA's intent or policy to regulate higher forms of life under TSCA.

EPA does not have primary authority to review the broader environmental consequences of substances not covered by FIFRA or TSCA. In those cases, the agencies involved have the authority and responsibility for review under the National Environmental Policy Act (NEPA). However, EPA has the responsibility to review assessments made by other agencies.

National Science Foundation

The National Science Foundation (NSF) currently funds research involving transgenic animals ranging from using recombinant DNA technology to transfer specific mouse genes between inbred strains—a more precise and rapid method to achieve the results

of traditional mouse breeding—to introducing genes for various growth factors between species with the hope of producing agricultural animals that grow faster and larger on the same or less feed. To date, NSF has supported such work only on laboratory animals and has not dealt with questions of large, domesticated animals. With the use of transgenic animals becoming central to whole lines of investigation, work with such animals is expected to expand as more genes are cloned and identified.

NSF is a research-oriented institution and not a regulatory agency, but it has endorsed the NIH Guidelines for Research Involving Recombinant DNA Molecules and the latest proposed changes to the guidelines. These guidelines, plus Federal standards for good animal practice, form the regulatory framework of NSF. All grantees must follow these guidelines and provide written documentation that they have abided by them. In addition, NSF requires all grantees to submit written documentation that they are abiding by Federal animal welfare regulations.

According to NSF, the essential reasons for regulating the use of transgenic animals are to prevent escape of any animal from an animal facility and to minimize possible escape from individual cages. It is NSF's position that the single most significant objective of control related to transgenic animals is to prohibit uncontrolled breeding between transgenic and conventional animals until the gene construction is well understood and the genotype recognized as desirable for continued research purposes.

Agency for International Development

Most of the Agency for International Development's (AID's) funding for research involving conventional and transgenic animals goes toward training personnel and to international research centers. These centers are financed by several donor countries. The United States provides only about 20 percent of the core budget in these centers. Accordingly, it has minimal control over research activities. In a related move, the NIH Recombinant DNA Advisory Committee is studying whether it has jurisdiction over the use of NIH-funded research in foreign countries.

In the relatively few cases where AID grantees are the direct contractors—for example, malaria vaccine researchers in U.S. universities—NIH guidelines are followed for health-related research, and USDA guidelines are followed for agricultural research. Grantees are required to file the appropriate notification with the corresponding agency. Transgenic animals imported into the United States would be reviewed under existing regulations in the appropriate agency (e.g., USDA/APHIS).

Fish and Wildlife Service (U.S. Department of the Interior)

The Fish and Wildlife Service undertakes selective breeding to manage and preserve species, such as to increase production at fish hatcheries, to enhance genetic diversity in species with reduced populations, or for standardized laboratory test animals. This work does not involve genetically altered animals in the context of genetically engineered, nonnaturally occurring populations. However, under extreme circumstances, it may be that the selectively bred genotypes are not represented in naturally occurring populations, but only in the laboratory.

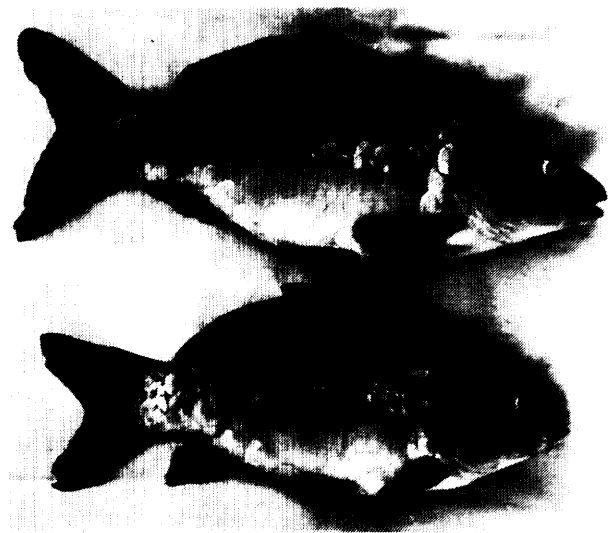


Photo credit: Rex Dunham, Auburn University

At top, a transgenic carp containing trout growth hormone gene; bottom, normal carp.

The Fish and Wildlife Service does not anticipate that it will have any uses of its own for genetically altered animals in the next 5 years. There has been some discussion of using transgenic fish to combat the effects of acid rain. The Fish and Wildlife Service does not consider this acceptable because altering target fish species alone would not maintain a healthy ecosystem and the present system would continue to degrade. Ecologically, it is better to try to attack the problem at its source rather than reconstruct an entire ecosystem to live with the consequences.

The Fish and Wildlife Service has several regulatory policies that relate to protecting the genetic integrity of wild stocks, the maintenance of natural habitat, and the protection of biological diversity. It also has authority over State regulations concerning the control or impact of migratory species, exotic species, or any fish or game species that crosses State lines. However, in most cases it lacks the authority to regulate the use of transgenic animals. Any involvement would require stretching the law and regulations meant for other purposes (15).

The Endangered Species Act could be used, for example, if a genetically engineered animal potentially affects a species protected by the Act. The National Environmental Policy Act also could be used to review or comment on Federal agency actions affecting the use of genetically altered species. Anything that might give a competitive edge to one species within an ecosystem could drastically alter the whole balance of the ecosystem.

National Aeronautics and Space Administration

The National Aeronautics and Space Administration (NASA) does not undertake or fund any research involving genetically engineered animals, and the Agency has no such work projected over the next 5 years. All NASA research involving animals follows NIH's guidelines.

U.S. Department of Energy

According to the Department of Energy's Office of Health and Environmental Research, no research is currently being supported in the area of genetically engineered animals. Genetically variant ani-

mals used by the Department have been developed through classical breeding programs (1).

SUMMARY

The U.S. Patent and Trademark Office in April 1987 issued a notice that "it considers nonnaturally occurring nonhuman multicellular organisms, including animals, to be patentable subject matter within the scope" of patent laws. The first patent on a transgenic animal was issued on April 12, 1988, assigned to Harvard University, for a mouse to be used in cancer research. The Patent Office policy has spurred debate regarding whether animals should be patentable subject matter.

The majority of animals likely to be patentable will be produced via microinjection or, eventually, other more precise recombinant DNA techniques. Such manipulations cannot, however, be considered to "violate species integrity" or "species barriers" in any meaningful biological sense. Manipulations now possible, contemplated, or likely in the foreseeable future are, in fact, less likely to disrupt the complex, coadapted gene complexes most often felt to be important to the formation and stability of species than practices of selective breeding used for decades or centuries.

Several Federal agencies regulate the experimental use or commercial development of genetically altered animals. Because current statutes regulate various uses and protections for animals, no single Federal policy governs all uses of genetically altered animals. In the absence of a single policy, Federal agencies will rely on existing statutes, regulations, and guidelines to regulate transgenic animal research and product development. Current federally funded research efforts may lead to patents on animals; however, the patentability of an animal does not affect the manner in which the animal would be regulated by any Federal agency.

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