USE OF ANIMAL MODELS IN MUSCULOSKELETAL RESEARCH

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ABSTRACT

Understanding of the human musculoskeletal system and common clinical disorders of bones, joints and soft tissues has been enhanced by the use of experimental animal models. Articles reporting on the results of these biomedical experiments frequently include conclusions that are based on the assumption that the biology of the animal model is similar to that of a human being for the disease process under investigation. The purpose of this investigation was to study the criteria and the considerations for selection of an animal model in musculoskeletal research. Selected journals from the musculoskeletal literature published between January 1991 and November 1995 were scrutinized for the use of animal models, and several criteria used in the selection of the various animal models were investigated. The selection criteria analyzed in this study included the biologic characteristics of the model, budget issues, the reproducibility of a musculoskeletal disease, and animal handling factors. A computer-assisted search of the musculoskeletal literature published from 1965 to 1995 was also performed to screen for reports comparing mammals used as animal models in terms of these selection criteria.

Our findings imply that the selection of animal models in research of the musculoskeletal system is based partly on non-standardized criteria that are not necessarily based on the biology of the disease process being studied. In addition, there are limited comparative data on the selection and use of different animals for musculoskeletal research. We believe the selection of models should be more standardized based on both biological and non-biological criteria. Researchers would then be able to put in a more meaningful perspective the results of research using animal models and their clinical implications.

INTRODUCTION

For thousands of years, it has been observed that animals served well for transportation, company, and nutritional supply. Mammals were also noted to share some remarkable morphological and physiological features with humans. Animal experiments were considered in Ancient times a fundamental scientific method to gain knowledge in biomedical research and education. Aristotle (384-322 BC) reported on scientific observations of flora and fauna. Some considerable misunderstanding for more than ten centuries of the normal human anatomy originated from Galen's dissections of pigs and apes. His writings were later rediscovered by the Arabs and then translated back into Latin. Andreas Vesalius (1514-1564) illegally studied the anatomy of fresh cadavers of lynched criminals and revoked some of Galen's findings. In 1878, statesmen legalized federal funding of medical research in the United States. John Cushing conducted experiments on dogs in 1900 in the Johns Hopkins Hospital. In 1915, a veterinary specialist was appointed as head of the animal lab at the Mayo Clinic. Although the National Institute of Health (NIH) was established in 1930, it was not until the Public Health Service Act of 1944 that the NIH became the leading biomedical complex and funding...
Use of Animal Models in Musculoskeletal Research

center in this country. In 1946, the headquarters of the National Society for Medical Research was established in Chicago. The number of animals used in experiments increased gradually from 1945 to 1965 and then declined afterwards (Figure 1). Veterinarians Nathan R. Brewer of the University of Chicago and Bernard J. Cohen of Northwestern University were instrumental in developing laboratory animal science after World War II. In 1957 and 1967, the associations for lab animal medicine and lab animal science (ACLAM and AALAS, respectively) were founded. Currently, over 500 veterinarians are board-certified in laboratory animal science. The contributions of veterinary medicine to human medicine and vice-versa have expanded our knowledge of pathology and biology. Several workshop conferences on potential research in comparative pathology held from 1961 until 1967 in Portsmouth, New Hampshire, enhanced our understanding of animal models. At the end of the 1960’s, a registry of comparative pathology was founded and a bulletin has been published since then.

This investigation was begun shortly after a lecture by a reputed orthopaedic surgeon a few years ago. The presentation at the time was a report of an expensive and exhaustive study on rabbit knees. Anterior and posterior cruciate ligaments were surgically sectioned and the rabbit knees were then submitted to continuous passive motion or were immobilized for several weeks. The harvested ligaments were subjected to histological studies and functional outcome analysis. The research results were then extrapolated to human clinical practice. For someone familiar with these lagomorphs, it is known that rabbit knees are almost continuously flexed. If not, the animal has splay-leg syndrome. The rabbit knee model thus seems to be biomechanically differ-

Musculoskeletal Literature Reviewed

- Acta Orthopaedica Belgica
- Acta Orthopaedica Scandinavica
- American Journal of Knee Surgery
- American Journal of Orthopaedics
- American Journal of Sports Medicine
- Archives of Orthopaedic and Trauma Surgery
- Bulletin - Hospital for Joint Diseases
- Clinical Orthopaedics and Related Research
- European Spine Journal
- Foot and Ankle International
- International Orthopaedics
- Iowa Orthopaedic Journal
- Journal of Arthroplasty
- Journal of Biomaterial Application
- Journal Bone and Joint Surgery - American and British Volumes
- Journal of Foot Surgery
- Journal of Hand Surgery
- Journal of Orthopaedic Research
- Journal of Orthopaedic Trauma
- Journal of Pediatric Orthopaedics
- Orthopaedic Clinics of North America
- Orthopaedic Review
- Orthopaedics
- Spine
- Unfallchirurgie
- Zeitschrift fur Orthopadie und Ihre Grenzbiete

Figure 1

Animals Used in United States for Scientific Purposes

Figure 2

Musculoskeletal Literature Reviewed

Volume 18 119
ent from a human knee. This prompted our investigation into the use of animal models in musculoskeletal research in an attempt to determine what criteria are used in the selection of a particular animal for study of a clinical condition.

MATERIAL AND METHODS
A Medline computer assisted literature search was performed on an arbitrarily chosen set of journals in the musculoskeletal and related literature published between January 1991 and November 1995 (Figure 2). A set of the most commonly used mammals in musculoskeletal research was then created and matched with the articles published in the selected journals to create a group of reports to be included in the study. All abstracts were placed in one of the following categories: reports on bone and cartilage healing, pharmacology, physiology, immunochemistry and grafting, biomaterials (prostheses, implants, cement, fixation), limb lengthening, infection, laser technology and tourniquet use, and imaging modalities.

A second Medline search was then performed on all studies published between 1965 and 1995 that compared different mammals as animal models for a particular condition. Also, information was gathered on the different pathological processes that occur in mammals and their similarities to those found in their human counterparts. Finally current government regulations, budget issues, and handling concerns involved in animal research were reviewed.

RESULTS
In our literature search, the mammals most commonly used in biomedical research were the rat/mouse, dog, cat, guinea pig, hamster, horse, cow, donkey, sheep, goat, swine, and nonhuman primates. A Medline search of the entire medical literature from 1991 to 1995 produced 201,989 publications using the aforementioned mammals (Figure 3). Forty-five percent used the rat as an animal model, 21 percent the mouse, and about 10 percent the rabbit. A search of the musculoskeletal literature revealed 601 articles using the same mammals during the same time period. Rats and rabbits were used in 62 percent of these articles, while swine, notorious for difficult handling, were used in only 1.5 percent of studies (Figure 4). Sheep were used four times more often and dogs three times more often in the musculoskeletal literature than in the medical literature overall.

Closer examination of the musculoskeletal literature revealed a number of trends. The study of the anterior and posterior cruciate ligaments was most commonly performed in rabbits or sheep. Osteoarthritis was extensively studied in rabbits via papain and Vitamin A
injection of knee joints, repetitive impact loading, limb denervation, prolonged immobilization, patellectomy, meniscectomy and ligament resection. In dogs, surgically induced articular cartilage defects, limb denervation and compression/immobilization were used to study osteoarthritis, while in bipedal rats the induction of osteophytes and compression/immobilization were utilized. Osteoarthritis research has also included mice, hamster, and guinea pig models. For the study of carcinogenesis, the rat was the most commonly selected model. Features of limb lengthening were most commonly investigated in the dog. The mouse was an often used model for osteoporosis research. Limb replantation and bone mineral content were investigated in the only six papers published utilizing nonhuman primates in the period between 1991-1995 in our selected list of journals. Finally, we noted a trend that English publications by Japanese researchers commonly reported on findings in rats, and German researchers frequently selected the sheep as an animal model.

A number of government regulations have had a significant impact on the use of animals in musculoskeletal research in recent decades. The Animal Welfare Act of 1966, amended in 1971, 1976, and 1985, was passed after considerable debate in the 1950's and 1960's. However, this original protective act did not include rats and mice. Therefore, this law was amended in 1985 and led to the creation of Institutional Animal Care and Use committees. The Good Lab Practice Regulations enacted by the Food and Drug Administration in 1978 provided additional protection from misuse and abuse of animals for research purposes. Furthermore, the American Association for Accreditation of Laboratory Animal Care was created to ensure that accredited care facilities meet reasonable and appropriate guidelines for the care of animals.

The Public Health Service Policy resulting from the Health Research Extension Act in 1985 created more strict guidelines for the use of animals in research than those outlined in the Animal Welfare Act. The Policy stated that an experiment "should be based on the knowledge of the disease or problem under study and so designed that the anticipated results will justify its performance." However, no specific criteria were provided to guide the selection of particular animal models for experiments. The American Academy of Orthopaedic Surgeons issued a position statement in 1987 on the appropriate use of animals in conducting biomedical and veterinary research. The organization stated that "research funds should be allocated within governmental and private research agencies to support the development of alternative approaches to animal research."

In addition to the influence of government regulation, budget restrictions and the growth of private industry were found in our investigation to play a significant role in the selection of animal models (Figure 5). The unit cost of each animal varied from two dollars for an outbred mouse to more than $1,500 for a rhesus monkey. The cost of nonhuman primates is compounded by the fact that these mammals require care in primate centers, which are also expensive. Furthermore, new regulations introduced by exporting countries, such as India in 1978, have decreased dramatically the import of primates to the United States from 126,857 animals in 1968, to 21,648 in 1980. Despite these regulations, nonhuman primates remain the most commonly imported laboratory animals. In regards to the increasing role of private industry, commercial firms are now able to deliver a vast array of services as well as special animal strains and variants. Extensive genetic linkage maps and a large selection of genetically identical inbred mice strains are available to expedite sophisticated genetic research.

One of the most important, if not the most important, factors involved in choosing an animal model was the ability of the animal to simulate human disease. Osteoarthritis has been shown to occur spontaneously in domestic animals including horses, swine, cattle and dogs such as German shepherds and Labrador retrievers. Degenerative joint disease has also been described in many strains of small laboratory animals such as mice (C57BL, STR/1N, NZY/B1, PN and BLO strains), hamsters and guinea pigs. Rats, however, with the exception of bipedal strains, display an unexplained resistance to the development of osteoarthritis.

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<tr>
<th>Unit Price of Selected Laboratory Animals*</th>
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<tr>
<td><strong>Rat</strong></td>
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<td>Mini-swine</td>
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<td>Nonhuman Primate</td>
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*Harlan-Charles River-HRP Inc. Catalog

Figure 5
Animal models were also found useful in the study of musculoskeletal oncology, metabolic bone disease, and other musculoskeletal diseases. The Swarm rat chondrosarcoma histologically closely resembles the well-differentiated types of human chondrosarcoma. Other animal models have been bred which develop rickets, age-associated osteoporosis and osteodystrophy. Rabbits may spontaneously develop osteosarcoma and transmit inherited diseases such as achondroplasia, spina bifida, scoliosis and osteopetrosis. Also, subclinical myopathy is a condition spontaneously occurring in guinea pigs. The dog has been used repeatedly in studies of hip dysplasia, achondroplasia and patella dislocation. They also display a striking resemblance to man in the development of osteosarcoma. Males are more often affected, 75 percent of the tumors affect the limbs and are located in the metaphysis, and less than 10 percent of dogs have metastases at presentation. The sheep, widely used for fetal research, has served as a model for muscular dystrophy, collagen dysplasia and sarcosomatetra.

Our second Medline search for publications comparing different animal models in musculoskeletal research published between 1965 and 1995 yielded very little information. Athanasiou et al. reported on significant interspecies differences in the mechanical properties of articular cartilage. Little else was found comparing various animal models in terms of their ability to simulate human disease.

CONCLUSION

Animal models continue to play an important role in the study of conditions that affect the musculoskeletal system of humans. In this study, we attempted to review the use of animal models in musculoskeletal research, identify the most commonly used animals, determine the criteria used to select a particular animal model, the cost, and the issues of regulation and care for the animals involved in using these models. Obviously, one of the most important factors in choosing an animal model is the ability of the model to reproduce a given condition in humans. Surprisingly, our literature search revealed very few studies comparing the ability of various animal models to reproduce human disease. Clearly, profound differences may exist at the gross, microscopic, and genetic level between humans and other mammals, and these differences must be appreciated before extrapolating the results of a given study to human clinical practice.

Our investigation indicates that results of experiments using animal models for the study of the musculoskeletal system frequently are extrapolated to human clinical practice without revealing limitations of the selected model. A multitude of non-standardized criteria may play an important role in the selection of the animal. It seems that there is considerable lack of comparative knowledge on mammals and other animals to guide the selection of an appropriate model for the study of the musculoskeletal system. We were unable to locate a centralized resource for this type of information. It may be desirable to develop a type of musculoskeletal registry for animal models in the future. This registry could incorporate knowledge derived from animal lab practice, comparative biology and veterinary sciences. A centralized database may aid in establishing standardized criteria for the selection of models.

Results derived from experiments utilizing animal models must always be viewed with caution because of the differences between species. However, significant gains in the understanding of parallel pathophysiology in humans can be achieved. It is our hope that the results of this investigation may enable researchers to put in a more meaningful perspective the results of research using animal models and their clinical implications.

REFERENCES


