



## Review Article

# Animal models in dental research – A review

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## ABSTRACT

Utility of animals for the service of mankind is practiced from time immemorial. In the era of scientific advancements, the use of animals has extended in to the research field as well. Numerous animal species are bred for research purpose in the laboratories and choosing the right animal for dental research remains a dilemma. This review throws limelight on the animal models available for dental research.

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## 1. Introduction

The first documented studies on animals dates back to 129 – 200 AD, when Galen, the great physician demonstrated the presence of blood in the arteries by using animal models. Since then animals models have been constantly used in bio medical research. Today animals are being specially bred in the laboratories for the same. Animal data can provide us with models of biologic trends before proceeding to human application.<sup>1</sup> Still most of the researches involving animals are done on vertebrates such as cats, mice, frogs, pigs, dogs, rabbits and primates.

Though animals appear different from humans, they share same systemic, physiologic and metabolic characteristics. Hence researches are conducted in animals for information that cannot be obtained from any other means or

to do clinical trials on drugs and other treatment modalities for testing the safety and efficacy before using on humans.<sup>2</sup>

## 2. Facets of biomedical research and use of animals

Any biomedical research can involve any of the three facets:<sup>3</sup>

1. Acquisition of new knowledge
2. Use of animals in teaching exercises
3. Testing of compounds, chemicals or devices for safety and effectiveness.

In all the three facets animal research contributes the major part. There are seven areas of medicine and biology where major animal experiments are handled.

1. Fundamental biological and medical research
2. Developing new treatments for diseases

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3. Preparations of natural products used in medical research and treatment
4. Safety testing of chemicals and drugs
5. Study of genetic disorders
6. Development of new diagnostic tests for diseases
7. In biology and medical education.

### 2.1. Animals used in research

Rodents and mice are the most widely used animal models. They make up for over 90% of the animals used in biomedical research. However, certain experiments need models at higher taxonomic levels. In such cases, higher mammals like dogs, cats, rabbits or nonhuman primates, models will be used. But all these animals comprise of less than 10% used in research.<sup>4</sup>

Again the animals basically can be classified as: small animal models and large animal models.<sup>5</sup> (Figure 1) According to Davidson et al, 1987, animal models are classified into four categories:<sup>6</sup> Experimental model, Negative model, Spontaneous model, orphan model. (Figure 2)

### 2.2. Non-human primates

Except the small size of teeth, non human primates have same deciduous and permanent dental formulas.<sup>1,7</sup> Commonly used non human primate models are: Howler monkey (*Alloutacaraya*), Squirrel monkey (*Saimirisciureus*), Cottonear marmoset (*Callithrixjacchus*), Cotton-top marmoset (*Saguinus Oedipus*), Cercopithecidae Baboon (*Papioanubis*), Rhesus monkey (*Macacamulatta*), Cynomolgus monkey (*Macacafascicularis*), Stump-tailed monkey (*Macacaac-toides*), Pigtailed monkey (*Macacanemestrina*), Hominidae Chimpanzee (*Pantroglodytes*) and Mountain gorilla (*Gorilla gorillaberingei*).<sup>8</sup> Smaller non human primates like squirrel monkeys are easier to handle, but their inflammatory profile is very different from humans. Other bigger non human primates are widely used in periodontal clinical research.

### 2.3. Hamsters

Very closely related to mice, the hamsters are used in periodontal and cariogenic research to study the disease characteristics. They are also models for studying disease transmissibility.<sup>9</sup> Hamsters have been used primarily for caries research due to the capability of the cariogenic microorganisms to form profuse amount of plaque and quickly develop carious lesions.<sup>8</sup> Unique feature of using hamsters in dental research is that both caries and periodontal disease could be evaluated *in vivo* at the same time.

### 2.4. Dogs

The periodontium of the dogs is the closest to humans. Periodontal diseases in the dogs closely mimic the disease

in humans. As with humans, gingival recession is an outstanding feature in dogs with periodontitis.<sup>10</sup> With regards to microbiota, there exists characteristic difference between humans and dogs. The subgingival microbiota in beagle dogs is mainly comprised of a high percentage of gram-negative bacteria. In disease, unlike humans there is an increase in catalase positive *Prevotella* species.<sup>11</sup> Hence dog models, particularly beagles are used in dental research for clinical surgical trials in Periodontology.

### 2.5. Ferrets

The domestic Ferret is a suitable model for the study of calculus because of its resemblance to human calculus. Interestingly the formation of calculus is not diet dependent as in the rat and hamster.<sup>8</sup>

### 2.6. Rodents

Rodents, belong to the same cohort such as mice and rats. Because of the advantageous smaller size, they are widely used in research. Other advantages of using rodents in dental research are low cost, known age and genetic background, controllable microflora, and ease of handling. Most of these models are restricted to oral microbiological researches as there is some possibility of some fundamental differences in host responses and divergence in the reaction of tissues to specific challenges between rodents versus humans.<sup>12</sup>

Recently the use of gnotobiotic or germ-free rat has been successful in understanding the pathogenesis of various oral diseases. Gnotobiotic rats of the Sprague-Dawley strain have been used to demonstrate the ability of various filamentous bacteria to form plaque and induce periodontal disease in the absence of other bacteria.<sup>13</sup>

## 3. Criteria for selection of proper animal models

Animal models selected for the research is based on various factors like the type of study, conditions unique to the animal that might complicate study, existing knowledge about condition or knowledge about unique response of the animal to study conditions. Laboratory constraints such as housing of large or non standard animals are also to be considered.<sup>6</sup> The selection or rejection of animal model should be based on the following criteria: Appropriateness as an analog, Transferability of information, Genetic uniformity of organisms, where applicable, Background knowledge of biological properties, Cost and availability, Generalizability of the results, Ease of and adaptability to experimental manipulation, Ecological consequences and the Ethical implications.<sup>6</sup> (Table 1)

### 3.1. Advantages of animal experiments<sup>8,13</sup>

Animal models have several advantages as compared to any other living models:

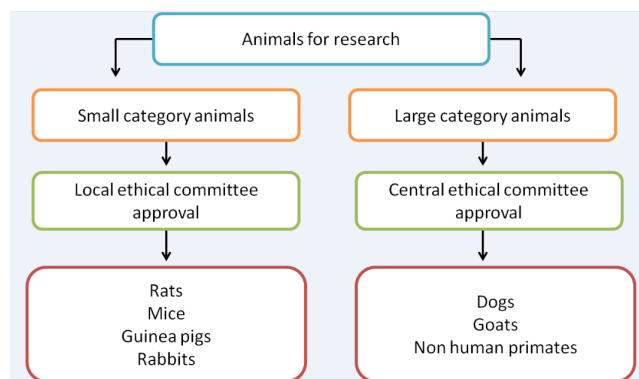


Fig. 1: Classification of animal models

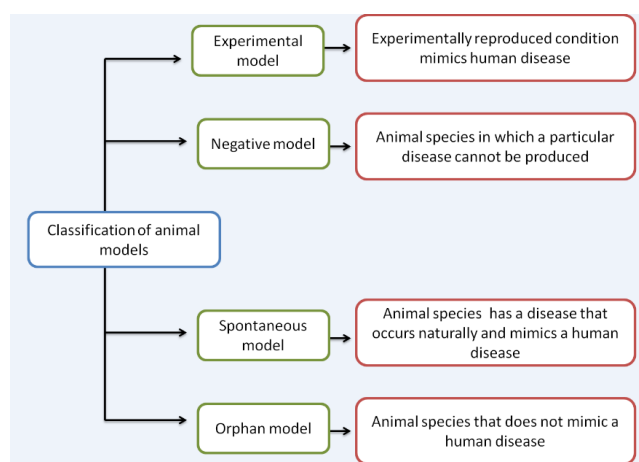


Fig. 2: Categories of animal models

Table 1: The 3 “R” approach

THE 3 “R” APPROACH
Replacement of animals with other methods
Reduction in the number of animal used
Refinement of project and the techniques used to minimize impact an animals

Table 2: Criteria for selection or rejection of animal model

CRITERIA FOR SELECTION REJECTION OF ANIMAL MODEL
Appropriateness as an analog
Transferability of information
Genetic uniformity of organisms
Background knowledge of biological properties
Cost and availability
Generalizability of the results
Ease and adaptability to experimental manipulation
Ecological consequences and the ethical implications

1. Long term maintenance of constant environmental conditions for research. This is very ideal for studying genetic defects.
2. To characterize the genetic - environmental interactions, various environmental conditions can be induced sequentially
3. Generation of complex pedigrees that are more powerful for genetic analysis is easier with animal models
4. Genetic hypotheses can be tested prospectively by selective mating.
5. Essential invasive and terminal experiments can be conducted.

3.2. Limitations of animal experiments<sup>8,13</sup>

1. Not all human diseases can be reproduced in animals.
2. All the conclusions derived from animal experiments may not be strictly applicable to human beings.
3. Difficulties are encountered in extrapolating findings from animal experiments in man.

3.3. Ethical considerations

There is always a greater concern about the rational and humane use of animals in research. This can be addressed by providing accreditation services to laboratories by constituting, National Accreditation Board of Testing and Calibration Laboratories (NABL) having membership of the International Laboratory.<sup>2</sup>

All medical research should be carefully planned, and this also includes medical research with animals. Experts who review a scientist’s proposed experiment involving animals weigh several considerations before approving each study. The most important thing is that the research must be relevant to human or animal health. Studies need to protect the animals’ welfare. As part of this research group, veterinarians assure the humane treatment of animals and provide medical and surgical support throughout research studies. Emergency veterinary care for research animals is available on a 24-hour basis.<sup>2</sup>

The following guidelines have been proposed by National Advisory Committee for Laboratory Animal Research, 2004 to reduce the impact on the experimental animals:<sup>14</sup>

The 3 R approach should always be considered. (Table 2)

1. Replacement with alternative methods.
  - Mathematical models
  - Computed simulation
2. Reduction in number
  - Minimum number required to validate the results should be used
  - Experiments on animals must not be repeated or duplicated unnecessarily.

3. Refinement of Projects and techniques used to minimize impact on animals

- Projects must be designed so as to avoid or minimize the pain and stress
- Appropriate measures like anesthesia, analgesia or sedation must be administered in procedures involving pain.
- Death as an end point must be avoided unless absolutely essential.

#### 4. Conclusion

There exists a wide range of animal models for various dental research. Each species has unique similarities and dissimilarities to humans oral environments. Choosing a animal model that is considered a gold standard, that which suits all fields of application is of utmost importance.

#### 5. Source of Funding

None.

#### 6. Conflict of Interest

None.

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