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Effective management of wistar rats in laboratory research: A Brief Review

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Abstract

Wistar rats (*Rattus norvegicus*) are one of the most widely used laboratory animals in biomedical research due to their well-documented genetic, physiological, and behavioral characteristics. The rats were originally developed at "The Wistar Institute" in the early 20th century and they have become indispensable models for studies in pharmacology, toxicology, genetics, and neuroscience. Optimal breeding practices, environmental enrichment, and strict health monitoring are critical for ensuring the well-being of the animals and the reliability of research outcomes. The rats are mostly susceptible to parasitic infections and zoonotic diseases. Additionally, ethical guidelines, such as the 3Rs (Replacement, Reduction, and Refinement), are fundamental to minimize animal suffering and also enhance research quality. Special attention is given to the importance of maintaining a controlled and stress-free environment for Wistar rats, as environmental stress can significantly affect their health and experimental results. Overall, proper care and management of Wistar rats are essential for the success of laboratory experiments and the advancement of scientific knowledge.

Keywords: Wistar rats, biomedical research, breeding practices, ethical guidelines, parasitic diseases

Introduction

Wistar rats (*Rattus norvegicus*), a widely used strain of laboratory rats, are indispensable models in biomedical research due to their well-documented genetic, physiological, and behavioural characteristics. First developed in the 1900s, Wistar rats have become one of the most commonly used species in laboratory studies, particularly in fields such as pharmacology, toxicology, neuroscience, and genetics. The development of Wistar rats, which includes the original inbred albino strain and numerous other strains, began at The Wistar Institute around 1909 and lasted into the 1940s. While the Institute sold the trademark for "Wistar" in the 1960s, the original Wistar rats still make up a large portion of the genetic lineage of laboratory rats today, with their descendants continuing to be used in laboratories around the world (Clause, 1998) [8]. The intentional development of rats into "standardized" laboratory animals began at the Wistar Institute in Philadelphia, aiming to meet the demands of scientific research and support the growth of the emerging scientific community (Clause, 1993) [7]. They are known for their calm temperament, ease of breeding, and well-established response to various experimental protocols, making them ideal subject for scientific investigations.

However, effective management is needed to ensure their significant role in biomedical research, to ensure the reliability and reproducibility of experimental findings. Proper care, handling, supplementation of nutritious feed, clean water and housing conditions are essential to minimize stress which promote the well-being of the animals. The factors such as environmental stress can have profound effects on their health and experimental outcomes as well (Lynch *et al.*, 2018, Meyer *et al.*, 2020) [15, 16]. For example, chronic stress in laboratory animals can result in altered endocrine function, immune response, and even genetic expression. Therefore, minimizing animal distress and ensuring proper housing, diet, and care protocols are fundamental for the integrity of laboratory studies. The optimal weight of a Wistar rat for experiments generally varies based on the type of research and the rat's age.

However, for most conventional laboratory studies, Wistar rats are typically used when they are about 6 to 8 weeks old, with their average weight ranging between 150 and 200 grams (as per National Institutes of Health).

The successful breeding and management of Wistar rats involve attention to various factors such as optimal mating age, appropriate mating systems, proper care during pregnancy, and effective management of offspring. However, breeding Wistar rats requires careful management to minimize genetic drift, ensure high reproductive success and prevent health issues that may arise from improper care or inbreeding. Controlling unwanted mating in Wistar rats during research play a crucial role to maintain the integrity of experimental results, prevent inbreeding, and ensure proper animal welfare. Unwanted mating can lead to complications such as genetic contamination, variability in experimental outcomes, or unintended pregnancies, which can disrupt the research process. Prior to the research, male and female rats should be separated in an ideal ratio to resolve the issue of unwanted mating.

Moreover, before commencing any research involving Wistar rats, researchers are required to submit a comprehensive research proposal to the Institutional Animal Ethics Committee (IAEC) or an equivalent body. The proposal should detail the research objectives, experimental methodology, and the intended use of animals. Furthermore, veterinary care is an essential part for maintaining healthy animals and ensuring reliable experimental results. This review provides a comprehensive overview of the scientific principles underlying the care and management of Wistar rats, aimed at optimizing outcomes in laboratory research.

Historical Overview of Wistar Rat

The Wistar rat, one of the most widely used laboratory animals, has a rich history that dates back to the early 20th century. It was first developed at the Wistar Institute of Anatomy and Biology at the University of Pennsylvania in 1906, where a colony of albino rats was established. The primary goal was to create a genetically uniform strain ideal for controlled laboratory experiments. The strain was selectively bred for traits like genetic consistency and calm temperament, making it suitable for a wide range of studies. By 1912, the Wistar rat had gained recognition, particularly

in genetics and medical research. As breeding techniques refined the strain, Wistar rats became pivotal in studies on diseases like cancer, cardiovascular issues, and infections. In the 1960s, commercialization expanded the use of the Wistar rat worldwide, even though the Wistar Institute sold the rights to the name "Wistarat." Its genetic homogeneity made it an ideal model for drug testing, neurological studies, and toxicology. Over time, the Wistar rat has contributed to numerous breakthroughs in medicine, including vaccine development and cancer research. In addition, Wistar rats are still fundamental to preclinical studies and regulatory testing, with their genetic stability and consistent responses to treatments making them an invaluable resource in laboratories across the globe (Heston, 1952; Chien & Wang, 2007; Wistar Institute, 2006) ^[9, 24].

Housing Conditions and Environmental Factors

Optimal housing conditions and environmental factors are essential for the health and welfare of Wistar rats, enabling them to thrive in laboratory environments and ensuring reliable research results. In the 1960s, wire-bottom cages were commonly used in laboratory settings for ease of maintenance, particularly for cleaning. However, these cages often caused foot injuries in the animals (NRC, 2011) ^[19]. As a result, solid-bottom cages were introduced in the 1990s, which typically included bedding, food, and water (Baumans *et al.*, 2010a) ^[4]. Today, there are various alternative housing systems available that better address the behavioural needs of rats and mice. These include cages with elevated tops and bi-level designs, which allow for natural behaviours such as climbing and rearing, while also offering areas for shelter. Figure 1, is providing an overview of standardise housing system for laboratory rats. Basically, ethological needs should meet as much as possible in housing conditions for laboratory animals during research period. Significant Knowledge regarding the existing guidelines on housing conditions and behaviour may be used to maintain the flow of research (Maghirang *et al.*, 1994) ^[25]. The specific conditions in which these rats are housed play a critical role in their overall well-being, influencing their physical health, behavioural patterns, and the consistency of experimental outcomes.



Fig 1: Ideal housing management of laboratory wistar rat

Essential factors for effective cage rearing

Wistar rats should be housed in clean, spacious cages with adequate ventilation. A minimum of 180 square inches of floor space per pair is recommended for good welfare.

Common cages include wire mesh or solid-bottom designs. Soft, absorbent bedding, such as corncob, paper, or wood shavings, should be used to promote comfort and cleanliness. Bedding should be changed regularly to

maintain hygiene and prevent ammonia buildup. According to studies, that rats favour low, dark cages, implying that the desire to avoid bright light outweighs the need for rearing space, with an optimal environment offering both shelter and room to move. Furthermore, the temperature should be maintained between 22-24°C (72-75°F) and a relative humidity of 40-60% (NRC, 2011) ^[19]. Wistar rats should be kept under a 12-hour light/dark cycle to maintain their circadian rhythms. Moreover, proper ventilation is an important factor to avoid the buildup of harmful gases such as ammonia (Tobin *et al.*, 2024) ^[23]. To maintain an optimal environment, the number of animals per cage should not exceed six to prevent overcrowding.

Management of nutrition and diet

Wistar rats require a balanced diet to ensure their health, growth, and reproductive success. Their standard diet typically consists of 18-25% protein, 50-60% carbohydrates, 5-10% fat, and 5-7% fibre. Essential vitamins such as A, D, E, and K, as well as minerals like calcium, phosphorus, and magnesium, are also included to support various metabolic functions. Supplementation of clean, fresh water must be available at all times, provided through water bottles with minimal contamination risks (National Research Council, 1995). Rats should always have access to clean water, with an average intake of 20-30 mL per 100 grams of body weight per day. Commercial diets, like Purina LabDiet 5001 or Harlan Teklad 8640, are commonly used as they are specifically formulated to meet these nutritional needs. For breeding rats, higher protein content (25-30%) and additional calories are necessary. Specialized diets may be provided depending on experimental requirements, such as high-fat diets for metabolic studies or increased protein for growth research. The feeding frequency is typically once a day, though it can be adjusted based on the rats' needs or specific study requirements. Maintaining a proper diet is crucial for obtaining reliable research outcomes and ensuring the well-being of Wistar rats (National Research Council, 2011, Olsson & Dahlborn, 2002) ^[20]. Hydration management plays a crucial role in any scientific study involving experimental animals, as it is essential for maintaining their health and ensuring reliable research outcomes.

Table 1: Nutrient requirement in Wistar Rat on daily basis

Nutrient	Amount
Protein	18-25% (from casein, soy, or other sources)
Carbohydrate	50-60% (corn, wheat, grains)
Fats	5-10% (vegetable oils)
Fiber	5-7% (necessary for gastrointestinal health)
Vitamins	5-7% (necessary for gastrointestinal health)
Minerals	Calcium, Phosphorus, Magnesium (Important for bone health)
Water	20-30 mL per 100g of body weight per day

Health Care and Monitoring

Effective health and care monitoring is crucial for maintaining the well-being of Wistar rats in laboratory environments, directly influencing the accuracy and credibility of research results. Consistent monitoring facilitates the early identification of health issues, ensures optimal living conditions, and supports the overall health and vitality of the rats throughout the study. Regular monitoring of body weight helps in tracking growth, as

deviations from normal growth patterns (sudden weight loss or gain) can indicate potential health issues (National Research Council, 2011). The condition of the coat, posture, and mobility should be routinely checked. Abnormalities such as rough fur or limping can signal health problems (Olsson & Dahlborn, 2002) ^[20]. Activity levels, feeding habits, and social interactions are key indicators of health. Changes in behavior, such as lethargy or aggression, should be closely observed.

Control of parasitic infestation

Regular access to a qualified veterinarian is essential to provide care and ensure the health of the laboratory animals. Laboratory rats are susceptible to a variety of parasitic infections, many of which are asymptomatic, though some can lead to significant health problems or immune suppression. These infections can disrupt the rat's physiological state, becoming unwanted variables in experiments. Therefore, rats that are free of parasites are mostly preferable for research purposes. Common parasitic infestations in Wistar rats are like *Syphacia obvelata*, *Aspiculuris tetraptera*, *Giardia muris*, *Isospora rattus*, *Eimeria spp.*, *Taenia taeniaeformis* etc. In addition, *Hymenolepis diminuta*, the "rat tapeworm" is also known as a zoonotic parasite (Ashtiani, 2008; Karuna *et al.*, 2013) ^[17]. Furthermore, one of the most common problem arises while rearing the colony of rat is infestation of Pinworms (*Syphacia muris* in rats) which leads to biological alterations in rodents, including modifications of growth, immune response and behaviour as well (Jacoby RO and Lindsey JR. 1997, Jacoby RO, Lindsey JR. 1998) ^[28, 29]. Although asymptomatic infected animals often affect data collected for studies. Usage of veterinary medicine like broad spectrum anthelmintic fenbendazole-medicated (FBZ) feed is a efficacious method to eradicate parasitic infestations from laboratory rats (Johnston NA *et al.*, 2006) ^[30]. A common administration schedule includes 7 days of medicated feed, then 7 days of unmedicated feed, with the cycle repeated 3 to 5 times (Huerkamp *et al.*, 2000) ^[26]. Moreover, FBZ-supplemented diet has no physiological side effect or toxic effect when administered in therapeutic dose (Joint FAO-WHO Committee on Food Additives 1991).



Fig 2: Parasitic infestation in liver of laboratory Wistar rat

Sites for blood collection in laboratory rats

Blood collection from laboratory rats is an essential procedure in research, requiring careful selection of the site to ensure the acquisition of quality samples while

minimizing harm to the animals. There are various sites commonly used for blood collection, each with its unique advantages and limitations. The tail vein is a commonly chosen site due to its easy accessibility and minimal invasiveness, making it ideal for repeated blood collections. However, it can only yield small volumes of blood, and repeated sampling may lead to damage of the tail. Frequency of blood collection is important. For studies requiring repeated blood collection, a temporary cannula can be used to minimize pain and stress in the animals. The jugular vein allows for larger volumes of blood to be collected but typically requires anesthesia to avoid distress. Cardiac puncture is typically employed when a substantial amount of blood is needed, and it is performed after euthanasia, as it is an invasive procedure that cannot be done on live animals (Beeton *et al.*, 2007) ^[31]. Retro-orbital

blood collection involves obtaining blood from the sinuses behind the eye, which is suitable for larger sample volumes (Figure 2). This method, however, necessitates anesthesia and can cause discomfort or injury if not performed properly. The saphenous vein, located on the hind leg, is less invasive and can be accessed without anesthesia, though the volume of blood collected is limited. Similarly, the femoral vein offers the possibility of collecting larger volumes of blood but also generally requires anesthesia (Frohlich *et al.*, 2018) ^[32]. Lastly, ear vein collection is another minimally invasive technique that is typically used for small blood samples. The choice of blood collection site depends on various factors, such as the required volume of blood, the frequency of collection, and the potential impact on the animal's well-being (Parasuraman *et al.*, 2010) ^[33].

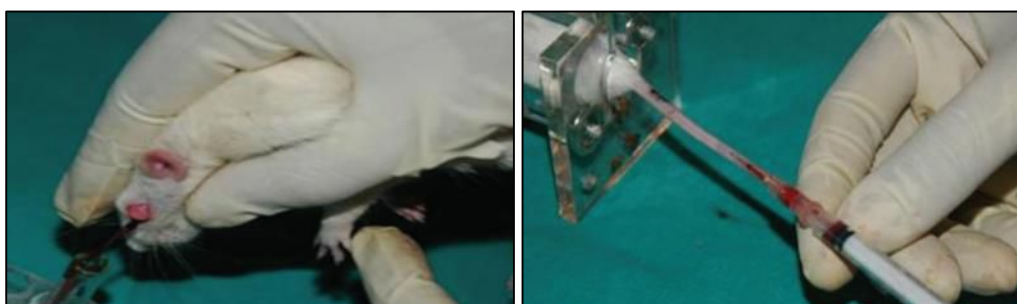


Fig 2: Blood sample collection from retro orbital and tail vein from Wister rat

Socialization and Enrichment

Socialization and environmental enrichment are critical for maintaining the well-being and natural behaviours of Wistar rats in laboratory settings. These practices not only improve the physical and psychological health of the animals but also ensure that the research results are more reliable, as they reduce stress and promote normal behaviour. Moreover, Wistar rats are social animals and should be housed in pairs or small groups to avoid isolation stress. Hence, group housing promotes social interactions and reduces anxiety among the group of animals (V. Bauman and PLP Van Loo, 2013) ^[2]. Furthermore, environmental enrichment, such as tunnels, nesting materials, chew toys, and running wheels, helps in reduction of stress and promotes natural behaviours. It has been proposed that continuous background noise, such as from a radio, may help in promoting breeding and reduce the animals' excitability. However, it is also possible that such noise could act as a source of stress for the animals (Baumans, 2010b) ^[4]. Studies have shown that rats respond to different sound patterns from a radio, with their reactions potentially varying depending on the specific strain of the rat (Krohn *et al.*, 2011) ^[14]. Handling of rats should be very gentle and consistent as well to minimize stress. Avoid rough handling, especially during experimental procedures.

Sexing

Sexing is nothing but identifying the gender of animal. By identifying the gender, animals can be segregated and unwanted pregnancies can also be controlled in-case of Wistar rats. Sex determination in mature rats can be easily done by inspecting the perineal region. Males typically have a noticeable scrotum positioned between the anus and the preputial opening, with the penis often visible and larger than the female's urethral papilla. Additionally, the anogenital distance, which is the space between the anus and

genital opening, is longer in males compared to females. In addition, sex discrimination is one of the most difficult step in prepubertal rats but also it is possible even in neonates (Otto *et al.*, 2015) ^[21].



Fig 4: Determining the sex of female and male Wistar rats under laboratory conditions (Source: Google).

Breeding management in Wister rats

Breeding management plays a major role in rearing Wistar rats in a laboratory setting for experimental purposes. The type of research being conducted determines the specific requirements for the animals, including whether pregnant females, males, or females of a particular age are needed. To maintain optimal physiological conditions, the first step after receiving the animal stock is to segregate the animals based on gender to control unwanted breeding as well. Wistar rats can be bred by introducing a female to a male during estrus. Pregnant females should be given extra bedding and a quiet environment during pre- and post-partum condition. However, after birth, ensure that all pups are nursing and active as well. Winning of pups from the

mother should be done at 21 days of age if required by the experiment.



Fig 5: Pups of Wistar rats in laboratory condition (Andersen ML and Tufik S (Eds.), 2015) ^[1]

Management of cleaning and hygiene

Cleanliness of cages is essential to prevent the spread of infections and zoonotic diseases. Therefore, cages should be cleaned regularly, typically once a week, or more frequently if necessary, especially when the rats are diabetic, to avoid the buildup of ammonia from the bedding material. Disinfect cages and equipment with appropriate, non-toxic agents (Rosenfeld *et al.*, 2012) ^[22]. Proper hygiene practices, such as wearing gloves and washing hands thoroughly, are important to prevent cross-contamination as well.

Ethical Consideration and experimentation

The development of Institutional Animal Care and Use Committees (IACUCs) is closely linked to the history of animal welfare regulation in the United States. Before 1963, the responsibility for animal care was primarily left to individual researchers, leading to inconsistent standards and practices across laboratories. In 1961, a group of veterinarians established the Animal Care Panel, which led to the publication of the first edition of "The Guide for the Care and Use of Laboratory Animals" in 1963. This guide, was later supported by the National Institutes of Health (NIH) and published by the Institute for Laboratory Animal Research of the National Academy of Sciences. The Guide has since been updated, with the eighth edition currently in use. Researchers are required to obtain ethical approval before beginning any experiment. This involves submitting detailed experimental protocols to an Institutional Animal Ethics Committee (IAEC) or equivalent, which reviews the study to ensure it complies with ethical standards and legal regulations (National Research Council, 2011). Ethical guidelines for the use of laboratory animals, including Wistar rats, are set by regulatory bodies such as the Institutional Animal Care and Use Committee (IACUC) in the United States, the European Commission's Directive 2010/63/EU in Europe, and the Animal Welfare Act. These guidelines emphasize the 3Rs principle:

- **Replacement:** Whenever feasible, animals should be replaced with alternative models, such as *in vitro* methods or computer simulations.
- **Reduction:** The number of animals used by improving experimental designs should be minimized.
- **Refinement:** Modify experimental procedures to minimize animal suffering and enhance their welfare.

Research involving Wistar rats must comply with ethical standards and be approved by an institutional animal care and Use Committee (IACUC) or similar body (National

Research Council, 2011). Experimental procedures such as injections, surgeries, and behavioural testing should be conducted with minimal stress, and proper anaesthesia should be used when necessary. Sacrifice the animal by following the guidelines of IACUC to perform minimal cruelty.

Conclusion

Wistar rats are essential models in biomedical research, widely used in fields like pharmacology, toxicology, neuroscience, and genetics due to their consistent genetic traits, docile nature, and reproducible experimental responses. For obtaining reliable research outcomes their effective use in laboratory studies by ensuring proper care and management is critical step. Factors such as appropriate housing conditions, nutrition, health monitoring, and ethical practices are integral to maintaining the well-being of these animals. In addition, optimal housing that provides adequate space, clean bedding, and controlled environmental conditions contributes significantly to the physical and behavioural health of Wistar rats. Providing balanced nutrition, clean water, and appropriate socialization further supports their overall well-being, promoting ideal conditions for research. Ethical guidelines, such as the 3Rs (Replacement, Reduction, and Refinement), play fundamental role which is responsible use of Wistar rats in research. Institutional Animal Care and Use Committees (IACUCs) play a vital role in ensuring adherence to these standards, safeguarding animal welfare, and maintaining the validity of scientific findings as well. By adhering to best practices while rearing wistar rats, researchers can ensure that their studies are both scientifically robust and ethically sound, while promoting the well-being of the animals involved.

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