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The Laboratory RAT

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dedication

P.E.S. To my father, James L. Sharp and Jamie Weaver, a childhood friend. “This one goes out to the one I love...This one goes out to the one I left behind” (REM).

M.L.R. In appreciation to my mentors, colleagues, and researchers who have made my career as a laboratory animal diagnostician challenging, rewarding, and always enjoyable.

preface

The use of laboratory animals, including rats, continues to be an important part of biomedical research. In many instances, individuals performing such research are charged with broad responsibilities, including animal facility management, animal husbandry, regulatory compliance, and performance of technical procedures directly related to research projects. In this regard, this handbook was written to provide a quick reference source for investigators, technicians, and animal caretakers charged with the care and/or use of rats in a research setting. It should be particularly valuable to those at small institutions or facilities lacking a large, well-organized animal resource unit and to those individuals who need to conduct research programs using rats starting from scratch.

This handbook is organized into six chapters: Important Biological Features (Chapter 1), Husbandry (Chapter 2), Management (Chapter 3), Veterinary Care (Chapter 4), Experimental Methodology (Chapter 5), and Resources (Chapter 6). Basic information and common procedures are presented in detail. Other information regarding alternative techniques, or details of procedures and methods which are beyond the scope of this handbook is referenced extensively so the user is directed toward additional information without having to wade through a burdensome volume of detail here. In this sense, this handbook should be viewed as a basic reference source and not as an exhaustive review of the biology and use of the rat.

The final chapter, “Resources,” provides the user with lists of possible sources and suppliers of additional information, rats, feed, sanitation supplies, cages, and research and veterinary

supplies. The lists are not exhaustive and do not imply endorsement of listed suppliers over suppliers not listed. Rather, these lists are meant as a starting point for users to develop their own lists of preferred vendors of such items.

A final point to be considered is that all individuals performing procedures described in this handbook should be properly trained. The humane care and use of rats is improved by initial and continuing education of personnel and will facilitate the overall success of programs using rats in research, teaching, or testing.

the authors

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From 1980 to 1991, Dr. La Regina was on staff at St. Louis University in St. Louis where her duties included diagnostics and clinical rodent medicine. In 1991, she joined the staff of the Washington University.

Dr. La Regina has been an active member in ACLAM since 1980, having served on the Board of Directors and as an Officer in the organization. She has published on a variety of topics related to laboratory animal disease and has been an active co-investigator in the area of pathology.

acknowledgment

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contents

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important biological features

introduction

Taxonomy of the laboratory rat:
Kingdom: Animalia
Phylum: Chordata
Class: Mammalia
Order: Rodentia
Suborder: Myomorpha
Family: Muridae
Genus: *Rattus*
Species: *norvegicus*

Rats are thought to have originated in the area of Asia currently occupied by southern Russia and northern China. *Rattus rattus* (black or ship rat, 2n = 38) was well established in Europe by 1100 A.D. (following the Crusades), with *Rattus norvegicus* (brown rat, 2n = 42) commonly found in Europe in the 1700s. This recent reappearance followed thousands of years absence. Fossilized rat remains dating to the Pliocene and Pleistocene

periods were found in Europe. Until the writings of Giraldus Cambrensis (1147–1223), there was no distinction between the *R. rattus* and mice. The late arrival of *R. norvegicus* to Europe is offset by its ferocious nature, essentially eradicating the black rat from its former strong holds. Today, the black rat is restricted to areas near water, and the brown rat has conquered the planet because of its climatic adaptability and ability to parasitize human refuse.

Today's laboratory rats are the domesticated descendants of *Rattus norvegicus*. Albino animals were held and used for rat shows, and frequent handling is thought to have tamed these animals. By the 1800s these animals were used for breeding and neuroanatomy studies in the United States and Europe. It was in the late 1800s and early 1900s that individual stocks and strains had their beginnings.

The laboratory rat has been, and continues to be a mainstay of biomedical research. Both albino and pigmented animals are available. There are recognized differences between wild and laboratory rodents. For example, laboratory rats have smaller adrenals and preputial glands, earlier sexual maturity, no reproductive cycle seasonability, better fecundity, and a shorter life span than their free-ranging wild counterparts.

nomenclature

Rats fall into two basic groups depending on whether they are inbred or outbred. One generally refers to inbred animals as strains, and outbred animals as stocks. One develops inbred strains through at least 20 generations of brother–sister matings, whereas outbred stocks have less than 1% inbreeding per generation and have been maintained in a closed colony for at least four generations.

Different stocks and strains show variability in many biological parameters including hematology, clinical chemistry, and anesthesia response. This variability is also observed in stocks and strains from different suppliers, so one should exercise caution in changing suppliers during mid-study.

There are specific nomenclature guidelines, with assistance available in using these guidelines. One may wish to consult the following:

ILAR, National Research Council, 2101 Constitution Avenue, Washington, D.C. 20418, U.S.A. Telephone: (202) 334-2590, Fax: (202) 334-1687;

PALM Institute, N29 W4 2-1-215 Sapporo 001, Japan. Telephone: 81-11-746-3988, Fax: 81-11-746-6722;

Registry of Inbred Strains, Dr. Michael F.W. Festing, IRC for Human Toxicology, Leicester University, University Road, Leicester LE2 7RH, UK;

Rat News Letter, 2542 Harlo Dr., Allison Park, Pittsburgh, PA 15101, U.S.A., Telephone: (412) 487-4289;

Transgenic Animal Database, TABD Coordinator, Oak Ridge National Laboratory, PO Box 2008, MS 6050, Oak Ridge, TN 37831-6050, USA, Telephone: (615) 574-7776, Fax: (615) 574-9888;

The Jackson Laboratory, Bar Harbor, ME 04609, U.S.A., Telephone: (207) 288-3371, Fax: (207) 288-8982.

behavior

Rats are nocturnal animals with most activity occurring at night and in the early morning. Changing the light cycle permits rats and investigators to share peak activity periods. This 12-hour shift will require a 2-week accommodation period for the rat. Although there are strain differences, rats are typically non-aggressive, inquisitive, and easily trainable. Frequent handling encourages their non-aggressive nature as they adapt to new surroundings or experimental situations. Improper handling, nutritional deficiencies, and vocalizations from other rats can result in undesired behavior. Males are usually more aggressive than females and when striking, bite once. Rats feel most comfortable in small, dark, confined spaces; a behavior investigators may use as a reward. When designing experiments, it is important to understand the rat's coprophagic behavior and its potential impact on metabolic, drug, and other studies. Male rats, unlike mice, are unlikely to fight when housed together. Rats also differ from mice in their willingness and acceptance of single housing.

anatomic and physiologic features

This section briefly summarizes the anatomic and physiologic characteristics of the laboratory rat. Special emphasis is placed upon those characteristics which are unique to the rat. Table 1 summarizes the basic biological parameters of the rat.

TABLE 1. BASIC BIOLOGIC PARAMETERS

Parameter	Value
Lifespan (years)	2.5–3.5
Mammary glands	6 pr
Male body weight (g)*	450–520
Female body weight (g)*	250–300
Body temperature (rectal)	35.9–37.5°C 96.6–99.5°F
O_2 consumption (ml/m^2/g body weight)†	0.84
Body surface area (cm^2)	10.5 (bw in g)$^{2/3}$
Food intake (g/100 g bw/day)	5–6
Water intake (ml/100 g bw/day)	10–12
Gi transit time (hours)	12–24
Urine volume (ml/100 g bw/day)	5.5
Urine specific gravity	1.04–1.07
Urine pH	7.3–8.5
Total body water (ml)*	167
Intracellular fluid (ml)*	92.8
Extracellular fluid (ml)*	74.2
Plasma volume (ml)*	7.8

* Body weights will vary with stock or strain.

† Based on a 250 g rat.

Oropharynx

- Dental formula: 2 (incisors 1/1 canines 0/0 premolars 0/0 molars 3/3) = 16.
- The incisors grow continuously.
- Lack water taste receptors found in other animals.
- Lack tonsils.

Salivary glands

- Three pair of salivary glands: parotid, submaxillary (submandibular), and sublingual.
    - **Parotid —** The parotid salivary gland secretes a serous product, and consists of 3–4 lobes. The parotid gland extends ventrodorsally from behind the ear to the clavicle. The parotid duct opens opposite the molar teeth. The protein concentration (2%) of the saliva is unique.
    - **Submaxillary —** The submaxillary (submandibular) glands are mixed glands secreting a serous and mucous product. They are found in a ventral region between the mandibles and thoracic inlet. There are two types of secretory granules found in the submaxillary glands, one in the acinar cells and the other in the granulated portion of the secretory ducts. Secretory duct granules of immature animals contain substructures not found in adult animals.
    - **Sublingual —** The sublingual glands are the smallest of the salivary glands and secrete a mucous product. The rounded glands may be found at the rostral aspect of the submaxillary glands, and may be found embedded in them.

Note: Brown fat is found in the ventral cervical region, and one should not confuse this structure with salivary glands or lymph nodes.

Esophagus

- The esophagus enters the lesser curvature of the stomach through a fold in the limiting ridge of the stomach. The fold prevents rats from vomiting.
- The esophageal lining is entirely keratinized epithelium.

Stomach

- The rat's stomach has nonglandular and glandular portions separated by the "limiting ridge." The nonglandular forestomach has a lining similar to the esophagus.

Small Intestine

Small intestine lengths and transit times vary with the age of the rat. The length values listed below are adult averages. The authors wish to direct the reader to the discussion by Varga concerning the interaction among age, intestine length, and transit time.

- **duodenum**: 10 cm in length
- **jejunum**: 100 cm in length
- **ileum**: 3 cm in length

Large Intestine

- **Cecum —** The cecum is a thin-walled, comma-shaped pouch with a prominent lymphoid area found on the lateral aspect of the apex. Although the rat cecum does not possess an inner septa as seen in other rodents it has an inner constriction which divides the structure into apical and basilar sections. The lymphoid tissue is thought to be analogous to the vermiform appendix found in human beings.
- **Colon —** The colon has three divisions: ascending, transverse, and descending. The ascending portion has oblique mucosal ridges, whereas the mucosal folds of the transverse and descending regions have longitudinal mucosal folds.
- **Rectum —** The rectum is that region of the gastrointestinal tract found in the pelvic canal.

Liver

- Liver weight: 10.0 g/250 g rat.
- Liver volume: 19.6 mL/250 g rat.
- Bile flow: 22.5 mL/d/250 g rat.

- Consists of four lobes: median, right lateral, left, and caudate.
- The rat has no gall bladder.
- The bile from each lobe leaves via ducts. These ducts then form the common bile duct, which enters the duodenum approximately 25 mm distal to the pyloric sphincter.

Pancreas

- Consists of a lobulated, diffuse organ, extending from the duodenal loop to the gastrosplenic omentum. The pancreas has a darker color and firmer texture than the surrounding adipose tissue.
- The diffuse nature of the organ results in a network of ducts which coalesce into 2–8 larger ducts emptying into the common bile duct.

Urinary System

- Kidney weight: 2.0 g/250 g rat.
- Kidney volume: 3.7 mL/250 g rat.
- Rats, like other rodents, possess a unipapillate kidney, which consists of one papilla and one calyx and enters the ureter directly.
- Long and short nephrons are present.
- Only animal whose kidneys contain significant amounts of L-amino acid oxidase.
- Female urethral orifice is at the base of the clitoris.

Reproductive System

To distinguish males and females, note that males have a greater anogenital distance than females, and larger genital papillae (Fig. 1).

female

- Six pair of mammary glands — 3 thoracic, 1 abdominal, 2 inguinal.

Fig. 1. Note the greater anogenital distance in the preweanling male rat on the right compared to the female rat on the left.

- Uterus is bicornuate and duplex consisting of two uterine horns, two cervices, and one vagina.
- Hemochorial discoid placentation.
- A **copulatory plug** forms from semen coagulation following copulation. Specifically it forms from secretions of the vesicular and coagulating glands, filling the reproductive tract from the vulva to the cervix. It will remain for a few hours following copulation, and then will decrease in size and fall out.

male

- Inguinal canal remains open throughout the animal's life.
- No nipples.
- Has an os penis.