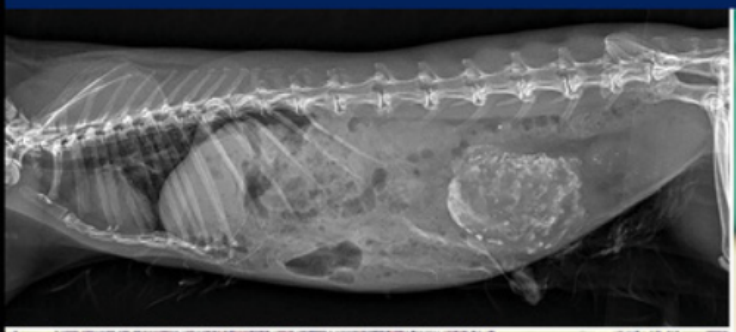
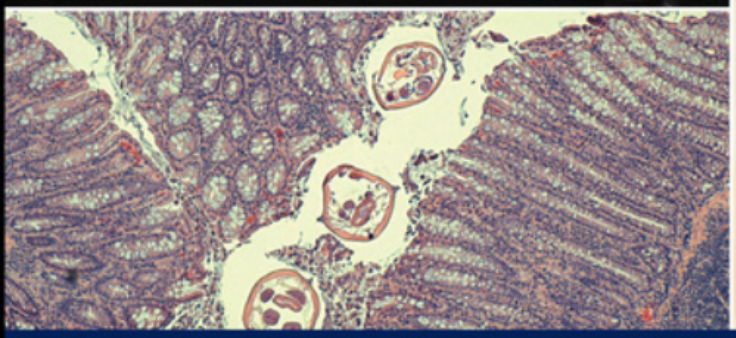
Sixth Edition

Harkness and Wagner's Biology and Medicine of Rabbits and Rodents

Patricia V. Turner • Colette L. Wheler • Hugues Beaufrère
Niora Fabian • John E. Harkness







American College of Laboratory Animal Medicine

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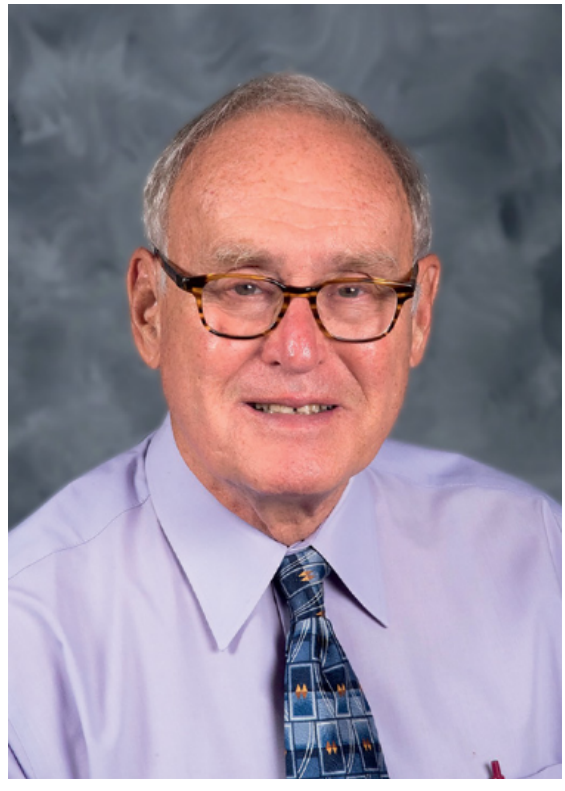
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This edition is dedicated to a devoted colleague and friend,
Dr John Harkness, 1939–2020.



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CONTENTS

Preface ix

Acknowledgments x

About the Authors and Illustrators xi

Chapter 1. Introduction, General Husbandry, and Disease Prevention 1

Introduction 1

Sources of Information 2

Taxonomy and History 3

Behavior 3

Regulatory Considerations 4

Genetically Modified Animals 4

Welfare-Friendly Clinical Practices for Rabbits and Rodents 6

Equipment Needs 7

Major Husbandry Concerns 8

Factors Predisposing to Disease 15

Allergies to Rabbits and Rodents 16

References 17

Chapter 2. Biology and Husbandry 21

The Rabbit 21

The Guinea Pig 45

The Chinchilla 57

The Hamster 65

The Gerbil 74

The Mouse 81

The Rat 93

Chapter 3. Clinical Procedures 104

Sample Collection 104

Hematology, Clinical Chemistry, and Urinalysis 116

Medical Imaging 130

Ophthalmology 135

Administration of Drugs and Formulary 142

Anesthesia 147

Analgesia 169

Surgery 174

Dental Procedures in Rabbits and Rodents 183

Quality Assurance Programs for Colony Health Surveillance 186

Other Special Techniques 189

Euthanasia 192

Chapter 4. Clinical Signs and Differential Diagnoses 196

Recognizing Signs of Illness and Pain in Rabbits and Rodents 196

The Rabbit 199

The Guinea Pig 210

The Chinchilla 219

The Hamster 221

The Gerbil 227

The Mouse 230

The Rat 236

Summary of Zoonotic Conditions of Companion Rabbits and Rodents 243

Chapter 5. Specific Diseases and Conditions 245

Acariasis (Mite Infections) 245

Anorexia and Reduced Food Intake 254

Astrovirus Infections 256

Bordetella Bronchiseptica Infections 256

Cestodiasis (Tapeworm Infection) 258

Coccidiosis (Hepatic) in Rabbits 260

Coccidiosis (Intestinal) 263

Coronavirus Infections 264

Corynebacterium Kutscheri Infections 269

Cryptosporidiosis 270

Dermatophytosis (Ringworm) 272

Encephalitozoonosis 273

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Enteritis and Related Conditions 276
Epilepsy in Gerbils 284
Filobacter Rodentium Infections (Cilia-Associated Respiratory Bacillus) 285
Gastrointestinal Stasis in Rabbits 286
Hantavirus Infections 288
Heart Conditons 290
Heat Prostration 291
Helicobacter Infections 292
Hematuria and Pigmented Urine 294
Hepatitis E Infections in Rabbits 295
Herpesvirus Infections of Rabbits 297
Hypovitaminosis C (Scurvy) in Guinea Pigs 298
Lawsonia Infections (Proliferative Ileitis/ Enteropathy) 301
Listeriosis 302
Liver Lobe Torsion in Rabbits 303
Lymphocytic Choriomeningitis Virus Infection 303
Malocclusion and Dental Disease 305
Mastitis 307
Mousepox (Ectromelia Virus) 307
Murine Encephalomyelitis 309
Murine Mycoplasmosis 310
Murine Norovirus Infections 312
Myiasis (Fly Strike)—Primary 313
Myiasis (Fly Strike)—Secondary 315
Myxomatosis 315
Nasal Dermatitis (Sore Nose) in Gerbils 317
Neoplasia 317
Nephrosis 322
Oxyuriasis (Pinworms) 324
Parvovirus Infections 326
Pasteurella Multocida Infections 328
Pediculosis 331
Pneumocystosis 332
Pododermatitis 334
Pregnancy Toxemia 336
Rabbit Viral Hemorrhagic Disease 337
Rabies Virus Infection 339
Ringtail 339
Rodentibacter Complex Infections 340
Rotavirus Infections 342
Salmonellosis 343
Sendai Virus Infections 345
Spironucleosis 346
Staphylococcosis 348
Streptococcus Pneumoniae Infections in Rodents 350
Streptococcus Zooepidemicus Infections in Guinea Pigs 351
Transmissible Colonic Hyperplasia in Mice 352
Tularemia 353
Tyzzer's Disease (*Clostridium Piliforme* Infection) 354
Ulcerative Dermatitis (Moist Dermatitis) 356
Urolithiasis 357
Venereal Spirochetosis (Treponematosis) 359

Chapter 6. Case Reports 361

The Rabbit 361
The Guinea Pig 363
The Chinchilla 366
The Hamster 367
The Gerbil 367
The Mouse 368
The Rat 369
Suggested Solutions 369
Rabbits 369
Guinea Pigs 375
Chinchillas 377
Hamsters 379
Gerbils 380
Mice 381
Rats 383

Index 385

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PREFACE

The *Biology and Medicine of Rabbits and Rodents* provides concise, up-to-date, reasonably comprehensive information to anyone concerned with the health, care, and management of rabbits and rodents. The book is intended for veterinarians, students, technicians, scientists, breeders, and those with a background in the biological sciences. A basic knowledge of biology and an interest in rabbits and rodents as pets, production animals, or laboratory animals are assumed. Beyond this, the emphasis throughout is on the practical aspects of rabbit and rodent care and health, and substantial detail is provided about many aspects of biology and husbandry, clinical signs and procedures, and specific diseases and their diagnoses. Distinctions between animals maintained for production, research or as companions are provided when relevant.

This book is intended to bridge the gap between the highly comprehensive hardcover reference works on various species of laboratory animals and a variety of class notes, handbooks, proceedings, autotutorial materials, and other publications used as references in practice or for teaching. The care and use of rabbits and rodents has changed considerably since the last edition of this text. The goal when writing this edition was to retain the easy-to-read practical style characteristic of previous editions, but to expand discussion of management and diseases that have evolved significantly since 1995.

Dr John Harkness, a close colleague and one of the original authors of this book, passed away during revision of this addition. We greatly appreciated his gentle but witty edits and corrections, as he challenged us to preserve the flavor and accessibility of previous editions. Every effort was made to correct errors and omissions from previous editions, and we welcome suggestions for improving and updating the next edition. Undoubtedly, despite our best intentions, errors will be discovered, and for these we apologize. We hope the new material added to this text will be helpful to new and seasoned readers of previous editions.

The major changes in this edition include revising certain disease descriptions under new taxonomic classifications; adding descriptions of new diseases, refined techniques such as quality assurance methods for rodent colony surveillance, conceptualization of research animal behavioral management programs, adding a section on welfare-friendly clinical practices, updating clinical techniques including anesthesia, analgesia, and pain recognition and management, and revising husbandry practices. The following diseases and conditions have been given new or expanded coverage: anorexia and dental disease, various enteric conditions of rabbits and rodents, heart disease, and adding new information on astrovirus, rabbit herpesviruses, hepatitis E of rabbits, and rabbit viral hemorrhagic disease. In Chapter 6, some case reports have been deleted, others modified, and new ones added. Many, many references have been eliminated or updated and some web-based resources have been included. Finally, over 150 images have been added to this edition, and almost all images are now in color.

We are humbled to have had the pleasure of working on the new edition of this classic text that has enjoyed such a loyal following over the decades. We can only hope that readers will be satisfied with our efforts, and that the information contained on the following pages will be used to improve the welfare of these interesting species that have contributed to human lives in countless positive ways.

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Many portions of this sixth edition of *Biology and Medicine of Rabbits and Rodents* have been rewritten and updated, and we are grateful to our colleagues in veterinary practice and animal care facilities for advancing the knowledge underlying many of these changes. We feel very fortunate to have had the opportunity to work together during the preparation of this material, and we learned a tremendous amount from each other. We gained a true appreciation of the depth and variety of knowledge that we all acquire during our diverse experiences working with these species in different environments, and would encourage all readers to take advantage of their peers and colleagues when seeking answers to small mammal cases. We recognize that in spite of our best efforts, errors may be present in the text, and we invite your comments for future editions.

During the preparation of this book we experienced loss of a colleague, loss of family members, ill health, and other challenges that delayed finalization of the text. We especially wish to recognize the support given by our families and thank them for their unfailing patience throughout this project. We also thank our editors at Wiley for their support and suggestions throughout the preparation of this edition.

This project was undertaken by the American College of Laboratory Animal Medicine (ACLAM), and all proceeds from book sales will be used to support the educational mission of the ACLAM Foundation.

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Colette L. Wheler is a veterinarian and worked previously as an Associate Professor, Zoological Medicine at the Western College of Veterinary Medicine, University of Saskatchewan, teaching veterinary students, caring for exotic pets, supervising the wild bird clinic, and providing veterinary services to the Saskatoon Zoo. In 2002, Dr Wheler left her position to become Assistant Director of the Animal Resources Centre and was heavily involved with administering the University of Saskatchewan's animal care and use program and providing care for its many research animals. Subsequently, Dr Wheler worked for the Vaccine and Infectious Disease Organization (VIDO) in Saskatoon, where she continued to provide humane care and oversight to a diverse group of research animals as Program Manager of Veterinary Research Services. Dr Wheler retired from her position at VIDO in June 2023 and spends her time travelling, gardening, reading, and bird watching.

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Hugues Beaufrère received his veterinary degree from the University of Lyon, France. Following veterinary school, he completed a small animal internship in a private practice in Belgium, an avian and exotic medicine internship at the Ontario Veterinary College at the University of Guelph, Canada, and a combined PhD/Zoological Medicine Residency program at the School of Veterinary Medicine, Louisiana State University and the Audubon Nature Institute in New Orleans. After the completion of his PhD, Beaufrère returned to the University of Guelph as an Assistant Professor in Clinical Studies. Beaufrère joined the School of Veterinary Medicine at the University of California, Davis in 2021 as an Associate Professor in Companion Zoological Medicine and Surgery. He is board certified by the European College of Zoological Medicine (Avian), the American Board of Veterinary Practitioners (Avian), and the American College of Zoological Medicine (subspecialty: Zoological Companion Animals).



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Chapter 1

Introduction, General Husbandry, and Disease Prevention

INTRODUCTION

Populations of rabbits, rodents, and other small mammal pets are difficult to estimate; however, a 2017 study conducted by the American Veterinary Medical Association (AVMA) estimated that more than 13% of US families keep these species as companion animals, including approximately 3.2 million rabbits, 1.4 million guinea pigs, 1.1 million hamsters, and 470,000 gerbils. However, only about 1.8% of these owners obtain annual veterinary care for their small mammal companions.

Numbers of animals used in research are also difficult to determine because of the limitations of applicable surveys and estimates where fixed data do not exist. Based on United States Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) data, approximately 107,000 hamsters, 197,000 guinea pigs, and 144,000 rabbits were used in the United States in research, testing, and teaching in 2021, whereas many fewer numbers of gerbils and chinchillas were used. The numbers of rats and mice used are significantly more difficult to estimate because these data are not collected or reported by US federal agencies. Approximately 1.3 million mice were used in Canada in 2022, and this accounted for 38% of animals used in research (www.ccac.ca). Estimates of mice used in the United States in biomedical research range from 6 to 20 million mice per year. It is even more difficult to find accurate references for numbers of rats used annually in research, although estimates of up to four million have been suggested. Mice and rats are typically thought to account for up to 85% of all animals used in research in the United States, although significant numbers of fish, poultry, swine, and cattle are also used for food and fiber research. Availability of genetically characterized strains and stocks with increased relevance to the diseases being studied, sequencing of the mouse and rat genomes (completed in 2002 and 2004, respectively), development of new transgenic technologies, and ease and economy of housing large numbers of animals have significantly contributed to the popularity of rodents as models for many aspects of biomedical research.

Rabbits are the third most common farmed animal species in the world with almost one billion slaughtered annually, and global production increased by almost 10% between 2008 and 2018. In 2020, China accounted for ~38% of world production of rabbit meat with approximately 314 million rabbits produced annually, followed by Europe at 20% with 117 million rabbits (http://faostat.fao.org/en). Both the United States and Canada account for a negligible amount of world rabbit meat production. Production is by and large proportional to per capita consumption, as rabbit meat is rarely exported from North America; however, increasing amounts of rabbit meat are being incorporated into premium companion animal feeds, necessitating import of frozen rabbit meat from outside of North America. Specific legislation covering meat rabbit production and welfare is lacking in many countries, including the European Union and China, although a new rabbit code of practice was published in Canada in 2018.

With the exception of China, the number of rabbits used for fur, felt, and pelt production is much lower than the number raised for food consumption. Rabbit pelts harvested at slaughter for meat are typically of poor quality, as breed, age at harvest, time of year, and husbandry conditions differ significantly for optimal production of meat compared with pelts. Rex rabbits are the primary breed used for pelt harvest, whereas angora rabbit hair is brushed and shorn regularly for yarn production and weaving. China is the world's largest producer of rabbit pelts and angora fiber today, but the industry lacks national welfare oversight and standards, bringing into question the ethics of angora fur production.

Chinchillas have been used by humans as a source of pelts for clothing for centuries, a practice that drove them to near extinction in the wild in the early twentieth century. In 1983, it was estimated that the United States led production of chinchilla pelts, but by the late twentieth century, South American and eastern European suppliers significantly outpaced US and Canadian production. The industry is decreasing in size with a global estimated production of 80,000 pelts in 2023. Public perception about the use of animal pelts for fashion has led to

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development of specific industry husbandry guidelines as well as US state bans, and other country bans on fur farming.

While veterinary care is relevant for all the aforementioned reasons, the subjects of this book—rabbits, guinea pigs, chinchillas, hamsters, gerbils, mice, and rats—are becoming increasingly popular as companion animals. As a result, veterinary practitioners should expect to see them as patients, regardless of whether they work in exotic specialty practices or more traditional veterinary animal clinics.

Certainly, the human–animal bond applies regardless of animal size, and companion rabbit or rodent owners are often frustrated in their attempts to find veterinarians who are knowledgeable about their small mammal companions. Problems of management and husbandry are often at the root of several disease conditions and can often be addressed by appropriate client education. Small mammal practice does require a modicum of special knowledge; however, careful extrapolation of experiences from other small animals (i.e., dogs and cats) to rabbits and rodents is often useful and appropriate. Common disease conditions not encountered in dogs and cats must be understood though, before attending to small mammal species, such as specific gastrointestinal conditions, antimicrobial sensitivities, dentistry issues, and various infectious diseases, including some that are zoonotic. Small animal clinicians can become competent with most small mammal problems through continuing professional development, and practitioners inclined to develop a client base in this area should not be deterred because of a perceived lack of specialized veterinary training.

Veterinary clinicians are likely to encounter rabbits and rodents in a wide spectrum of situations, presenting a significant challenge when compiling literature regarding management of health and diseases of these species. For example, rabbits and rodents are produced by commercial breeders for the purposes of research and testing. Most animals raised in this manner are reared in specific pathogen-free (SPF) barriers that preclude introduction of disease agents, and they are sold to research establishments that maintain highly controlled environments for housing these animals. Because of the sophisticated nature of some research, these animals are usually defined physiologically, genetically, and microbiologically. In contrast, rodents and rabbits in the retail pet trade have less certain genetic identification and health histories, and are often managed in ways that do not limit disease transmission among species and conspecifics, including mixing of species from different sources in large distribution centers. Commercial breeding operations for food and fiber production are intermediate between these two scenarios, emphasizing production as a goal, and employing management schemes that result in yet a third spectrum of disease issues. For example, in rabbits, the prevalence of certain diseases tends to be radically different between companion, laboratory, and meat animals. Therefore, medical challenges for private practitioners evaluating small mammal pets are substantially different from those seen by institutional laboratory animal veterinarians, and veterinarians treating animals in meat or fiber operations.

Early literature describing the attributes of these species originated from the laboratory animal and commercial breeder industry; however, more recent texts have been developed with the private practitioner in mind, adopting an individual animal approach versus a herd health approach to treatment. Although the biology, physiology, and disease susceptibility of animals reared and kept for research or as companion animals are similar, differences in purpose and management requirements should be kept in mind when reviewing the available literature on these animals. For example, housing requirements for mice held in a laboratory animal facility emphasize environmental and microbiological controls for the sake of experimental uniformity. These standards may exceed practical recommendations for owners rearing fancy mice for show or breeding rodent prey for reptile feeding. Diseases described in the laboratory animal literature are typically those seen in specific strains and ages most commonly used for research (i.e., SPF, genetically defined stocks of rodents, and New Zealand white rabbits) and are likely to differ substantially from common conditions of rodents purchased at the local pet store, chinchillas managed in a production setting or neutered geriatric house rabbits. Treatment of animals reared for food or fur production may be limited due to the impact of drug residues or damage to pelts. Thus, it is important to use professional judgment when evaluating the literature and to consider the differences in management and purpose when formulating an appropriate diagnostic and therapeutic plan for each case.

SOURCES OF INFORMATION

References for veterinarians who see rabbits and rodents in private practice are readily available. Web resources abound, but should be regarded with some caution if unreferenced or not evidence-based. LafeberVet (lafeber.com/vet/) is a useful, free online resource for veterinarians that requires an initial registration and provides excellent articles and videos on treating exotic companion animals, including small mammals. General references related to the practice of rabbit and rodent medicine are listed at the end of this chapter. Species-specific references are provided in the other chapters. This text emphasizes general references and indices of current literature rather than exhaustive literature reviews.

Knowledge about rabbits and rodents varies considerably among veterinarians. Even among the most knowledgeable and successful practitioners, recommendations for treatment vary, depending on personal experience and geographic area of practice, which may determine the nature of conditions seen as well as the general availability of therapeutics with which to treat different conditions. The Veterinary Information Network (VIN, www.vin.com) is a subscription-only online network that supports dialogue among veterinary practitioners,

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including specialists in rabbit and rodent medicine. Membership in VIN also provides ready access to a searchable literature, webinar, and case database that includes many exotic species. Laboratory animal veterinarians have extensive training in these species, particularly in matters relating to biology, husbandry, and disease. Diagnostic laboratories specializing in rodent and rabbit diseases also can be helpful in suggesting appropriate work-ups or providing necropsy and specialized diagnostic services. Companion animal veterinarians may need to seek diagnostic laboratories that specialize in research rodent or rabbit health monitoring for specific testing of certain infectious agents, because many laboratories geared to domestic animals do not provide these tests. Similarly, diagnostic expertise and availability of specific, validated assays for use in meat or fur-bearing species is limited.

TAXONOMY AND HISTORY

Detailed taxonomy and history of domestication of rabbits and rodents can be found in Chapter 2. Until the early 1900s, rabbits and rodents were classified similarly; however, anatomic and physiologic studies indicated significant differences leading to reclassification of rabbits in their own distinct order. Rabbits are members of the family Leporidae in the order Lagomorpha, whereas rodents are members of the order Rodentia. Rats, mice, gerbils, and hamsters are in the suborder Myomorpha ("rat-like," a clade of Myodonta), while guinea pigs, degus, and chinchillas are classified in the suborder Hystricomorpha ("porcupine-like," a clade of Ctenohystrica). Differences in classification of rabbits and rodents relate to jaw musculature, dental anatomy and physiology, as well as to differences in nutrition, gastrointestinal function, reproduction, and molecular data. Rabbits and rodents belong to the monophyletic clade of the Glires.

Rabbits and guinea pigs have been used for food (and domesticated to the extent of captive production for this purpose) for centuries; however, during the last century, breeding of these species, as well as of chinchillas, commenced for other purposes. This included the widescale production of pelts (rabbits, chinchillas), use in biomedical research (primarily rabbits and guinea pigs), and as fancy show animals. Whereas mention is made of domestication of mice in Asia as long ago as 1100 B.C., modern fancy rats and mice were first domesticated in the late nineteenth century. Though rats were occasionally used for food in times of famine, their initial domestication was for the once popular sport of rat-baiting, in which several rats were placed in a pit and bets collected on how long it would take a terrier to decimate the captives. Fancy rats and mice are relatively popular, and are judged in shows based upon size, color, and behavior. As discussed, rats and mice are the predominant mammals worked with in biomedical research; development of inbred and outbred stocks in the early twentieth century preceded the current explosion of genetically engineered strains (see below). Hamsters and gerbils were more recently domesticated and were introduced as companion and research animals in the 1950s. All these species became popular as small mammal companions starting in the 1960s, concurrent with their availability in pet stores and from private breeders, and with growth of urban and suburban communities.

BEHAVIOR

An understanding of the natural behavior of these animals is essential if provision of appropriate husbandry and veterinary care is to be made. All of the species described in this text are prey species, and as such, they are generally stressed in the presence of a perceived predator, such as a cat or dog, and have developed adaptive behaviors to avoid predation. One of the most prevalent of these is the propensity for active behaviors to be concentrated either during the dark phase of the daily cycle (nocturnal activity), or during dawn and dusk transitions (crepuscular activity). This is most apparent in hamsters, which exhibit significant resistance to arousal during the light cycle, and is least apparent in guinea pigs, which scatter their activities over a 24-hour period. This fact may limit the ability of a clinician or owner to evaluate normal activity, in that the typical physical exam and evaluation will occur when the animal is less likely to be active, and may not be exhibiting evidence of pain. Behavioral evaluations are further complicated in that the "fight or flight" response initiated during an exam may override behaviors less conducive to overall survival. For this reason, evaluation during the dark phase and in the home cage can be beneficial for detecting subtle abnormalities. Evaluation in the home environment is often possible in a laboratory situation, and may be feasible when evaluating a colony-wide problem at a commercial breeding establishment. If animals must be moved from their normal area to an examination area, it is helpful to have a small, darkened, secure transport cage and to minimize sudden and loud noises in the area of the cage. Many practices have developed procedures for specifically accommodating these small mammal companions; for example, restricting appointments to times when no predator species will be present or partitioning waiting rooms (see below for welfare-friendly practice recommendations for small mammals).

Rabbits and rodents have highly developed senses of smell and hearing to aid in detection of predators. Therefore, it is likely less stressful to examine and house these animals outside the sight and smell of perceived predators. Prey species are often approached from above by predators, thus when picking up an animal, a slow, steady approach from the side will allow orientation to the movement. Rabbits and rodents are often calmed by a confident and encircling grasp, and by covering the eyes. This can be achieved by use of a towel or sleeve during the examination process.

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In general, the amount of stress that may be induced by even minimally invasive clinical procedures should always be weighed against the benefit of intervention in rabbits and rodents to a far greater degree than is typically considered for dogs and cats. Stress can be minimized by thoughtful consideration of their natural behaviors, and by calm manipulations that take these behaviors into consideration.

REGULATORY CONSIDERATIONS

Rabbits and rodents worked with in biomedical research are subject to significant regulatory oversight. In the United States, the Animal Welfare Act (AWA), a Federal law promulgated by the Animal Welfare Division of USDA-APHIS, outlines provisions and standards expected for rabbits, guinea pigs, chinchillas, hamsters, and gerbils, as well as other mammals worked with in biomedical research. Rats of the genus *Rattus* and mice of the genus *Mus* specifically bred for use in research are exempt from AWA coverage. In 1998, USDA-APHIS issued a regulatory update advising that any retail pet store selling small mammals be licensed as a dealer subject to AWA regulations.

The Health Research Extension Act (HREA) provides standards for all vertebrate animals used in biomedical research funded by the United States Public Health Service (including the National Institutes of Health, Centers for Disease Control and Prevention, and Food and Drug Administration). Specific measures of the HREA are outlined in a document published by the National Academies Press (NAP) under the auspices of the Institute for Laboratory Animal Research (ILAR), a division of the National Research Council (NRC), entitled *The Guide for the Care and Use of Laboratory Animals,* and often referred to as "The Guide." Laboratory animal veterinarians, and those acting as veterinary consultants to facilities using animals in biomedical research, should be well versed in this document. This and other guidelines for use of animals in biomedical research are referenced at the end of this chapter.

Regulations regarding the use of laboratory animals also exist in many other countries, such as the UK, the E.U., Japan, and Australia. In Canada, the Canadian Council on Animal Care (CCAC) has developed guidelines for the care and use of animals in science. All vertebrate species, as well as cephalopods, are covered by these guidelines (www.ccac.ca). Any research institution holding animals and receiving Canadian federal funds for research must comply with CCAC guidelines and participate in periodic on-site assessments of their facilities and operations. Participation is optional for private institutions not receiving federal monies, but many organizations choose to comply with the CCAC guidelines to demonstrate a high level of commitment to humane animal care and use. The CCAC also has produced species-specific guidelines in recent years that detail specific requirements and expectations for care and housing of various animals, including rats and mice. Other small mammal species-specific guidelines may follow in the future.

Regardless of the national framework of regulatory oversight, many countries around the world, including the United States and Canada, have a requirement for a system of local ethical research oversight in the form of an Animal Care Committee or Animal Welfare Body. The main purpose of these bodies is to review the care and to safeguard the use of all animals housed in a facility for scientific purposes.

There is minimal specific legislation anywhere in the world that deals with the welfare requirements of rabbits raised for meat or rabbits and chinchillas raised for fiber and fur production. Whereas country-specific general transportation and slaughter regulations and guidelines apply to all animal species, rabbits are often combined with poultry when considering commercial production, with little regard for species-specific physiologic and behavioral differences and requirements. Canada has published and implemented a Code of Practice for the Care and Handling of Rabbits (http://www.nfacc.ca/codes-of-practice/rabbits), and this topic is also receiving increased attention in the E.U. by the European Food Safety Authority (EFSA).

GENETICALLY MODIFIED ANIMALS

Animals have been selectively bred for centuries to develop genetic characteristics desired by humans. Since the 1980s, advances in recombinant DNA technology have greatly accelerated the capacity to manipulate the genome of domesticated species, including that of mice, rats, and rabbits. This has been especially significant in mice, which have robust stem cells and blastocysts (early embryo stages) that are readily manipulated. In 1982, the first report of a genetically engineered mouse ("transgenic mouse") was demonstrated by inserting a growth hormone gene into the germline of an inbred mouse, resulting in an altered phenotype. Animals with the gene inserts weighed two to four times more than their nonmanipulated inbred siblings, providing a dramatic example of the utility of this technique. Further developments of this technology, and subsequent refinement of more sophisticated methods for specific gene targeting such as activation, deactivation or replacement with an experimental gene, have resulted in propagation of many thousands of strains of mice used in laboratory studies for investigations in such varied fields as infectious and congenital diseases, development and differentiation, toxicology, cancer, immunology, and neurobiology. Mice altered by one of these several methodologies are collectively known as genetically modified mice (GMM) (see Table 1.1 for examples).

The first widely used technique developed for insertion of foreign DNA into the germline of an animal was microinjection. With microinjection, early embryos (blastocysts) are

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Table 1.1. Examples of some genetically modified mice (GMM) including production methods and uses in biomedical research.

Type of Modification	Procedure for Creation	Phenotype/Example
Oncogene expression, e.g., myc or ras	Microinjection	Expression evaluated in tissues for studies of tumorigenesis
Immune system alterations	Knockout or Clustered regularly interspaced short palindromic repeats (CRISPR)	Interferon, cytokine, interleukin or specific immunocyte knockouts with specific immunodeficiencies
Regulation of gene expression	Microinjection or knockout or CRISPR	Regulatory element mutations used to study fetoprotein expression
Creation of animal models of single-gene mutations	Knockout or CRISPR	Cystic fibrosis resulting from disabling cystic fibrosis transmembrane regulator gene in mice
Creation of models for study of HIV-AIDS	Microinjection	Mutated HIV transgene develops Kaposi's sarcoma skin lesions in mice
Development of sensitive tests for toxicologic screening	Microinjection or knockout or CRISPR	Mice expressing a marker gene with a disabled promoter region; reversion of the promoter to an active form following exposure to potential toxicants can be screened in vitro following tissue harvest

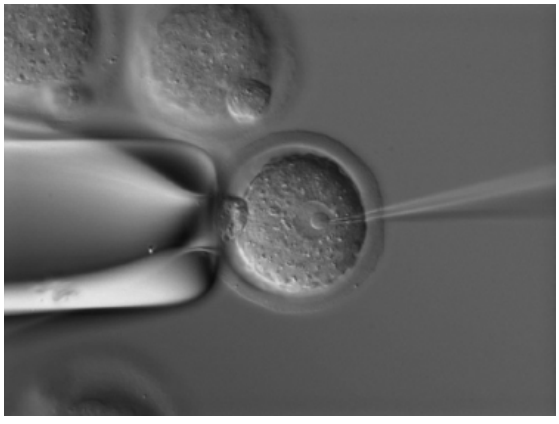


FIGURE 1.1. DNA being injected into an embryonic nucleus by microinjection. Courtesy of A. Bower and M. Baetscher.

removed from the female mouse and then, using a specialized microscope, a fine glass pipette is used to pierce the cell membrane and inject prepared DNA into one of the embryonic nuclei (Figure 1.1).

The injected embryos are then surgically implanted into another recipient female and pups are delivered at term and reared by the mother. Offspring are typically tested at or around weaning for evidence of incorporated microinjected DNA sequences. An experienced laboratory produces pups from 30% to 60% of injected embryos; 10–40% of these will be transgenic. This technique results in random insertion of multiple copies of DNA sequences (1–200 copies) into the mouse genome. Multiple rounds of breeding ensue onto an inbred strain to develop stable homozygous lines, which are then used for further experimental manipulations.

More sophisticated knock-out technologies were later developed using methods that specifically impair or insert new genes into a designated site within the genome. Two important discoveries preceded this technology: (1) the ability to grow mouse embryonic stem (ES) cells in culture, and (2) understanding the process of homologous recombination during DNA replication. Undifferentiated ES cells have the capacity to develop into any cell of the body when provided with appropriate cues; in the case of knock-out development, this includes mixing the stem cells with an early-stage embryo (blastocyst). Commonly, segments of DNA with the altered gene of interest are mixed in a culture with mouse ES cells. Cells are subjected to an electrical field that opens pores in the cell membrane (electroporation). Some of the electroporated ES cells take up foreign DNA; following cell division, homologous recombination occurs between the ES genome and foreign DNA in a small fraction of cells, resulting in inactivation of the gene of interest. Cells that have undergone recombination are selected, microinjected into blastocysts, and implanted into recipient female mice. A percentage of offspring will be born as chimeras, that is, with cells of both the wild-type embryo and the altered ES cells, and these can be detected visually if the ES cells and blastocysts are each generated from mice of different coat colors (Figure 1.2).

Genetic testing and breeding will eventually result in genetically characterized stable mouse lines. Experienced laboratories will produce approximately two lines per DNA targeting sequence attempted; it takes a year or more for this success. Even more sophisticated GMMs are being produced that conditionally express certain genes, allowing studies of the effects

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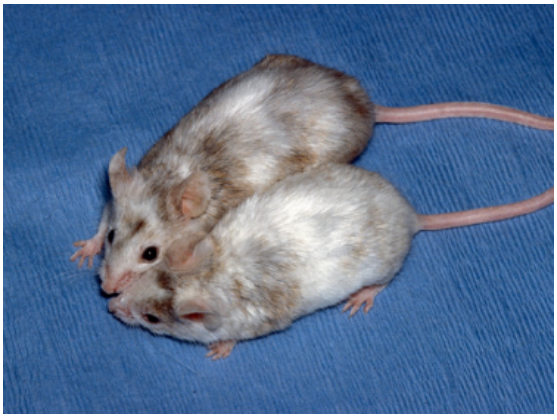


FIGURE 1.2. Two chimeric mice produced by knock-out technology. Courtesy of K. Pritchett-Corning.

of "turning on" or "turning off" a gene in a specific tissue or at a specific developmental stage, for example.

The effects of genetic modification are unpredictable and may result in subtle phenotypic alterations that may not be clinically obvious. Clinical veterinarians and veterinary pathologists have played an important role in developing, standardizing, and cataloging mutant phenotypes, which in combination with complete genome sequences results in understanding of molecular and genetic contributions to physiology, behavior, and many disease processes.

Recently developed gene editing technology using the CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 (generally shortened to just CRISPR) systems allows for increased precision when modifying DNA. The technique is based on the adaptive immune system of bacteria and makes use of the Cas9 endonuclease, which can cut DNA at precise locations specified by a synthetic RNA guide. In addition to this highly selective editing, the process can significantly shorten the time to when genetically modified animals are available for research because it does not involve injecting foreign DNA.

These molecular and cellular manipulations have generated tens of thousands of GMMs that either need to be propagated at low levels to keep the line viable or preserved via cryopreservation of sperm, embryos, or ova for future use. GMMs may be immunocompromised, have reduced fertility, or have increased morbidity or mortality, resulting in the need for more sophisticated monitoring and veterinary intervention. Veterinarians play an important role in developing management practices that consider the special needs of these animals and are advocates for their welfare and appropriate care.

Genetic engineering of rats has been much more difficult to master, though recent advances in embryonic stem cell technology hold promise for solving some of the technical difficulties that have hampered development of these animals. The unique physiology and behavior of rats compared to mice make them very useful for certain studies, particularly in cardiovascular disease, neurobiology, and behavior.

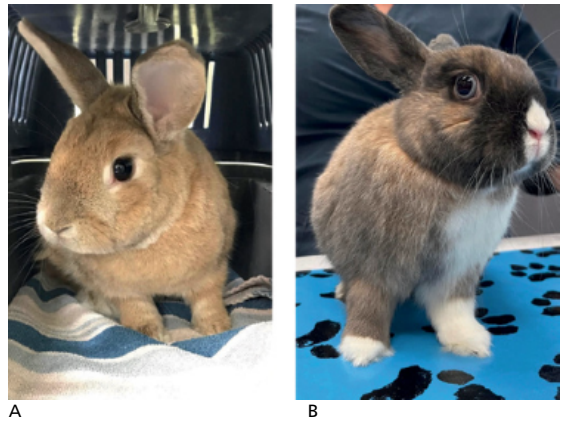
WELFARE-FRIENDLY CLINICAL PRACTICES FOR RABBITS AND RODENTS

Perhaps the most important consideration when working with companion rabbits and rodents in clinical situations is that they are prey species. With this in mind, many clinical practices, including those related to the overall clinic environment (e.g., waiting area, exam rooms, hospital ward), patient handling and restraint, physical examination, and clinical procedures, can be incorporated to reduce anxiety and enhance the welfare of these species.

Clinic Environment

It is important to optimize the client waiting area, exam rooms, and hospital ward for small mammals. Some clinics may specialize in or exclusively see small mammal pets or exotic companion mammals, such that avoidance of predator species is much more easily achieved. Rabbit/rodent-only clinics can operate similarly to those for cats, for example, with specific times of the day or week designated exclusively for these consultations. For mixed-species practices, it is important to provide a quiet seating area away from predator species such as dogs, cats, and ferrets, ideally with a visual barrier. Providing towels to cover carriers in the waiting area can help make rabbits and rodents feel more secure.

When possible, set aside an examination room exclusively for small mammal patients to minimize their exposure to predator odors. The exam room environment should be kept calm and quiet, and dimmer lights may be beneficial. Using a clean towel or nonslip mat on the table may help the animal feel more secure and will help reduce noise (Figure 1.3). Avoid excessively loud sounds (e.g., speaking volumes, background music, banging instruments) when examining the patient and be aware that the hearing ranges of these species can differ from that of humans.



A B

FIGURE 1.3. A: Example of suitable carrier for companion rabbit, B: Rabbit on a non-slip mat on examination table. Courtesy of CAEPC.

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For example, rodents and rabbits are adapted to hearing higher frequencies that people cannot hear.

Rabbits and rodents should be hospitalized in a secure room separate from potential predators, such as ferrets. Caging should be escape-proof and safe for both the patient and the handler. Specialized top-opening cages and incubators designed for small mammal pets are readily available. For short hospital stays, some rodents can be hospitalized in the familiar surroundings of their home cage. Standard hospital cages designed for dogs and cats can sometimes be adapted for rabbits, guinea pigs, and chinchillas, although care must be taken to prevent falls as the cage door is swung open. The cage can be provided with a towel or blanket brought from the client's home, and the floor can be lined with a nonslip nontoxic material to provide a comfortable surface, such as a rubberized mat with small crosshatches that provides traction while allowing urine and feces to pass through. A litter box is usually needed for rabbits, preferably with the same substrate used at home, and a shallow resting tray with hay, shredded paper or other soft bedding can also be provided. A hide or shelter, such as an inverted tissue or cardboard box with an opening cut out, is essential for guinea pigs and chinchillas, and can also be used to facilitate restraint, as guinea pigs in particular tend to scatter when startled. Enclosures with mesh fronts that preclude animal escape and that can withstand chewing may be useful.

A supply of species-specific food pellets, good-quality hay, and critical-care formula for herbivores is needed for hospitalized rabbits and rodents. Providing fresh leafy greens and other vegetables may encourage eating. Owners should be consulted as to their pet's food preferences and can be asked to bring a small quantity of the animal's regular diet during periods of hospitalization to avoid gastrointestinal upset. Clean potable water should always be available, preferably in a hanging bottle to prevent soiling or in a non-tippable dish. An elevated dry area should be available as a refuge from damp bedding due to inadvertent leaking or spillage.

Physical Examination and Patient Handling

Clinic personnel must be competent in appropriate handling and restraint of rabbit and rodent companion animals to minimize stress and to avoid injury to the patient as well as the handler. Hands should always be washed thoroughly between patients, and a fresh lab coat should be worn if the last patient handled was a dog, cat, or ferret. The small mammal patient should be approached gently, quietly, and calmly. Recommendations for species-specific restraint methods are provided in Chapter 2. Rabbits, guinea pigs, and chinchillas have strong leg muscles and fragile skeletons, leaving them prone to fractures of their limbs, pelvis, or lower back. For this reason, it is especially important to handle and support them in a position that prevents them from kicking, jumping, or being accidentally dropped. Carriers that can be opened from above are often preferred to give the broadest exposure to the whole animal and ensure that the animal is aware of your presence.

The examination should begin by first observing the patient in its enclosure, focusing on its activity, mentation, respiratory rate and effort, as well as the appearance of any feces and urine present. Next, obtain the patient's body weight and use this opportunity to gauge the animal's temperament before performing the physical examination. Body weight is one of most important objective assessments of patient progress and is also essential for calculating appropriate doses of medications. Rodents are easily weighed in a container such as a plastic box or disposable paper bag or cup tared on a small digital gram scale. The carrier in which the patient is presented also may be used as the weighing container. Rectal body temperatures should not be obtained routinely as this may lead to excessive excitement.

Procedures

Fractious or distressed small mammals may benefit from mild sedation for examination or diagnostic testing. Extra caution must be taken when sedating sick or debilitated patients. Procedures such as blood draws that may be routinely performed on a conscious dog or cat may not be well tolerated in small mammal pets without sedation or anesthesia. For example, venipuncture in an awake guinea pig can be inherently difficult, and manual restraint for such a procedure can be very stressful for the patient. Therefore, sedation or anesthesia may be required.

In general, if the animal is alert enough to defend itself vigorously, it will tolerate sedation (with an appropriately selected drug protocol—see Chapter 3). Induction with gas anesthesia can be performed in a small induction box or inside a large facemask (for smaller patients), taking care to protect personnel from waste anesthetic gasses. Appropriate thermal support should be provided and body temperature should be closely monitored, taking particular care with heat-sensitive species, such as chinchillas, to avoid overheating.

EQUIPMENT NEEDS

Therapeutics and equipment available in a small animal practice can often be adapted for use in rabbits and rodents. Rabbits and cats are similar in size and can share some of the same equipment. Drugs, including anesthetics, and their dosages are discussed in other sections. Drugs must be used cautiously because virtually all use is extralabel in these animals. Very small dosages are often required, and it is sometimes necessary to carefully dilute the stock drug to generate a manageable injection volume. Appropriate diluent, storage conditions, and length of time the diluted drug is stable are important considerations, as is accurate labeling of the diluted drug. It is especially critical to be aware of use of drugs in meat rabbits to ensure that appropriate withdrawal times are followed prior to slaughter for human consumption.

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Rodents weigh between 18 and 20 g (2/3 oz) for a mature female mouse to approximately 1 kg (2.2 lb) for obese or pregnant guinea pigs. These species should be weighed in grams or kilograms, depending on the patient size. Scales with up to a 1–2 kg capacity and with sensitivity to 5 g are essential, as is an appropriate weighing container for the animal. Larger rabbits may require scales of up to 10 kg capacity. The tare function on digital scales allows automatic deduction of the weight of the container (box, pet carrier, clean disposable paper bag, or coffee cup) or towel/blanket, if needed for patient comfort, from the digital measurement. Obtaining an accurate body weight is very important, not only for correct dosing of small rodents and rabbits but also for detecting changes in body weight, which are often the only objective data available for monitoring these small mammals over time. Equipment adapted to patient size should also be used, such as small needles, miniaturized surgical instruments, magnification devices (surgical loupes, endoscopes), and anesthetic monitoring equipment of appropriate sensitivity (equipment designed for research animals or human neonatal and pediatric devices). Other considerations include: (1) the need to perform oral examinations and tooth trimming in a small and narrow oral cavity; (2) requirements for administration of volatile anesthetics to small animals with high metabolic rates; (3) maintenance of core body temperature during anesthesia; (4) physiologic monitoring of rapid heart and respiratory rate in a small patient during anesthesia; (5) availability of appropriate dentistry tools; and (6) dilution of stock drugs with appropriate diluents to avoid inaccuracies and overdosing. Some recommended specialized items include those listed in Table 1.2.

MAJOR HUSBANDRY CONCERNS

Maintaining high husbandry standards is essential for reducing or eliminating factors that predispose animals to injury, disease, or development of abnormal behaviors and stereotypies. This includes establishing satisfactory methods for sanitation and providing escape-free, appropriately resourced, well-constructed caging. These concerns extend to animal housing for pets, as well as to research and commercial production settings.

Behavioral Management Considerations

Housing and husbandry approaches should provide for the behavioral well-being and physical comfort of the animals. It should take into consideration the normal behaviors, postures, and typical movements of each species as well as considering opportunities for animals to engage more with their environment and with those who care for them. Taking a more holistic approach helps to ensure that we better meet the needs of these animals and that they have a good life. Regardless of their end purpose, whether as a companion animal, research subject or for commercial production, small mammals typically spend the majority of their life in close contact with the cage environment, and it is important to ensure that this environment is optimized. Animals housed in a suboptimal environment without sufficient space, choice, and control, and opportunities for regular exercise, exploration, and cognitive stimulation may become bored, fight among themselves, and develop abnormal behaviors detrimental to their health and well-being, such as fur chewing and bar biting. Although ensuring the absence of disease is an important concern when caring for these animals, consideration and attention to their behavior is also very important as it provides insight into their emotional state. An umbrella model has been proposed to explain the concept of a holistic behavioral management program for research animals, and this concept can be adapted to other settings in which small rodents and rabbits are kept and maintained (see Figure 1.4). Expanding an animal's options for performing species-typical activities and behaviors can positively affect both physiologic and behavioral well-being (Figure 1.5). Strategies to consider include adding objects to chew and manipulate, which encourage fine motor activity; novel foods, which provide opportunities for variation in diet and foraging; and other resources that stimulate senses other than touch or taste, for example, those promoting exercise. It is important that objects added be used and enjoyed by the animals, that they can be consumed, sanitized or discarded at regular intervals, and that they do not introduce safety hazards that may impair animal health. Examples of species-specific recommended resources are provided in Chapter 2.

Rabbits and rodents are highly social species and do best when housed in pairs or groups whenever possible with the exception of female and mature male hamsters, breeding does with kits, and intact male rabbits, which often fight with severe consequences when housed with conspecifics. Most of these small animals naturally dig tunnels and live in burrows in the wild, and should be housed on solid flooring with absorbent substrate and adequate nesting material.

Housing

Primary enclosures (cages and pens) should be structurally sound, appropriate for the species housed, in good repair, free of sharp or abrasive surfaces, built for easy cleaning, and constructed to prevent escape and intrusion of other animals. They should also be large enough to incorporate all needed cage furnishings and other resources as well as providing for freedom of movement and normal postural adjustments, such as eating, mating, stretching without touching the cage top, jumping, and exercising. Unpainted wood, untreated metal, and other porous or unsealed materials that are difficult to sanitize should not be used for long-term housing of rabbits or rodents. Flooring and nesting materials that prevent escape, provide the capacity to burrow and maintain thermoneutrality, and allow for adequate sanitation should be used. While

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Table 1.2. Special equipment needs for small mammal procedures.

A. Physical Examination/Blood Collection/Drug Administration Needs

Digital scales able to accurately weigh animals from 20 g to 10 kg
Towels/baskets/restraint devices (preferably dedicated to rabbits/rodents)
Small needles (22–28 gauge) and butterfly IV catheters
Small gauze pads and rolls, self-adhering elasticized bandages, medical tape
22–26 gauge IV catheters
Ball-tipped dosing needles—straight and curved (flexible plastic preferred) for oral gavage
0.5 mL, 1 mL, 3 mL, and various straight- and curved-tip syringes (low dead space syringes for blood draws and drug injections)
30 mL and 60 mL catheter tip syringes for feeding of rabbits
Microcollection tubes for blood samples (serum separator, heparin, ethylene diamine tetra acetic acid [EDTA])
Microtip swabs for microbiology culture
Otoscope with several sets of plastic cones for ear and cursory dental examinations
Small bivalve vaginal or nasal speculum with light
Sharp clippers (consider portable moustache clippers)
Pediatric stethoscope
Nebulization or oxygenation chamber
Small nail trimmer

B. Hospital In-Patient Needs

Secure caging with appropriate nesting and bedding material and environmental controls (preferably in a quiet ward or area separate from other species)
Food crocks that are difficult to tip over and have low sides for easy access
Water bottles with operational valves or sipper tubes
Food
- Herbivore critical care formula
- Different types of hay (timothy, oat, botanical, mixed, alfalfa)
- Species-specific pellets for rabbits and rodents
- Fresh leafy vegetables

Litter pans and litter appropriate for rabbits
Hide boxes, especially for guinea pigs and chinchillas

C. Anesthetic and Surgery Needs

Thermal support system (e.g., forced warm air system, water recirculating blanket, heating bags, microwavable heating pads), disposable hand warmers (also useful for vasodilation prior to blood collection)
Bubblewrap, tubular gauze, or stockinette for draping small rodents
Ophthalmic surgical or microsurgical instruments
Small metal wound clips (8 mm) and wound clip applicator
Appropriate gauge (3-0 to 5-0) suture materials with round/cutting/reverse cutting needles
Inhalant gas vaporizer with nonrebreathing assembly
Small face masks (commercially available or can be fashioned from syringe cases)
Small induction chambers (commercially available or can be made from appropriately sized plastic containers with rubber gasket seals)
Surgical restraint blocks
Small cuffed and uncuffed endotracheal tubes (2-0 and larger)
Transparent or light-weight paper surgical drapes
Curettes
2.7 mm rigid endoscope (for intubation)
Sterile cotton-tipped applicators
Surgical loupes (e.g., Surgitel®)
Appropriate size surgical retractor (e.g., Lonestar retractor®)
Micro-stream pediatric capnography
Pulse oximeter (designed for small mammal pets or research mice and rats)
Continuous temperature probe
Infusion pump

(*continued*)

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Table 1.2 (Continued)

D. Dentistry Needs
Cheek dilator/spreader
Rabbit/rodent mouth gag
Dental unit with straight hand piece and rotating dental burrs/soft tissue protector
Rabbit incisor luxator
Rabbit molar luxator
All-purpose dental scaler/curette
Cheek teeth extraction forceps
Tongue depressors
Topical anesthetic gel

E. Nice to Haves (a.k.a. "Bells and Whistles")
Radiologic and ultrasound equipment
Stereoscope for microvascular surgery
CT scanner for skull imaging
Dental radiography unit
Rabbit/rodent dental platform
Laryngeal mask airways (e.g., V-gel®)
Ventilators for exotic species (e.g., Vetronics small animal ventilator®)
Doppler unit and cuffs
Endoscopic and video-recording system
Radiosurgery unit and forceps
Mouse/rat intubation platform and instruments
Non-invasive blood pressure monitor

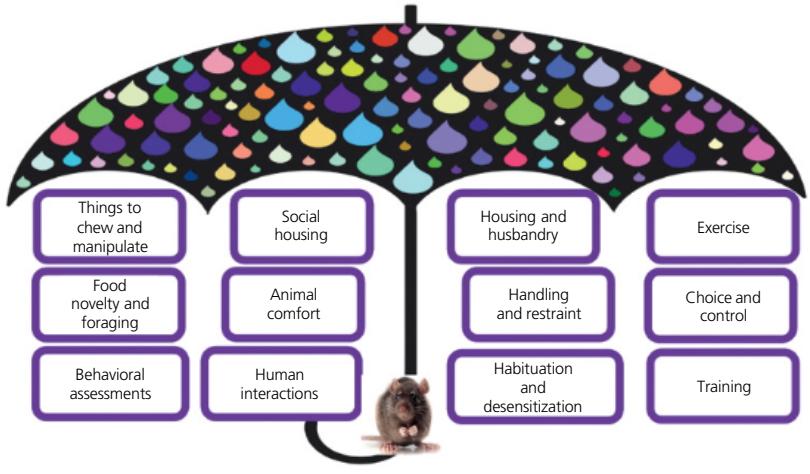


FIGURE 1.4. A proposed umbrella model of research animal behavioral management programs. Turner et.al., 1919 / MDPI / CC-BY-4.0.

wire or plastic mesh or perforated metal flooring is commonly used for meat rabbits to reduce disease burden and promote ease of sanitation, solid resting mats or surfaces are highly beneficial and promote animal comfort as well as reducing foot or hock lesions (pododermatitis, see Chapters 2, 4, and 5).

Physical Comfort

Animal caging should be dry, clean, well-ventilated but protected from drafts, and kept away from excessive noise and direct sunlight. Regulatory guidelines for institutional temperature and humidity ranges are provided within the US AWA, the ILAR Guide, and the CCAC guidelines (Table 1.3).

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FIGURE 1.5. Example of thoughtfully planned housing for gerbils.

In general, the thermoneutral zone of rodents is 26–30 °C (79–86 °F), and these animals are comfortable in warm ambient temperatures. Rabbits prefer cooler temperatures because of their dense coat and may be more comfortable at 16–20 °C (61–68 °F) temperatures. Rabbits can tolerate much cooler ambient temperatures provided they are protected from drafts and are given abundant dry bedding. Cages should never be placed in direct sunlight to prevent overheating of these animals, none of which have efficient cooling mechanisms. Hairless and smaller rodents, such as mice, require higher ambient temperatures. Relative humidity in the environment should be maintained between 30% and 70%. Temperature or humidity extremes and variations can significantly contribute to discomfort and disease susceptibility, and should be closely monitored.

Room air changes in institutional animal facilities, using fresh or filtered air, are generally required to be at least 10–20 complete air changes per hour, although more recently, there has been a move to more performance-based indicators of sufficient ventilation. These rates of air exchange are recommended to reduce waste gasses, airborne particulates, and allergen load associated with a large number of animals housed at high density in research or production settings. Fewer air exchanges are certainly adequate for small numbers of companion rodents or rabbits in private homes. The size of the room, strain and sex of animal, number of animals present, number of animals per cage, type of cage, and sanitization interval affect ventilation requirements. For companion small mammals, enclosed cages such as covered aquaria should be avoided, as these may result in poor air circulation and a build-up of potentially toxic levels of ammonia and carbon dioxide. Aquaria left in direct sunlight can also result in hyperthermia and rapid death. In research facilities, a light intensity of 30 foot candles (323 lm/m^2) at 1 m above floor level (approximately equivalent to a dimly lit office) is adequate for routine housing and is recommended by the ILAR Guide. Less light is needed to maintain circadian rhythms, and higher illumination intensity may induce retinal degeneration in albino rats and mice. Animals maintained under conditions of continuous light or dark may become infertile.

Housing for small rodents, particularly mice in research facilities, has generated a unique industry, as methods to house large numbers of animals efficiently while limiting spread of adventitious pathogens have become increasingly important. Filter top caging was initially demonstrated to provide effective cage-level barriers to the spread of disease in the 1960s; however, the modern caging systems now used widely were first introduced in the 1980s. The most economical microisolation system is static, that is, air circulation between the room and cage is passive. This leads to a rapid build-up of high levels of ammonia and CO_2, necessitating frequent (typically semi-weekly) cage changes. Individually ventilated caging (IVC, also known as ventilated caging systems or VCS) is now widely available commercially and has largely replaced static cages in many facilities. Several companies produce IVC with different specifications. These may have high efficiency particulate air (HEPA) filtration for incoming or outgoing air or both. The benefits of IVC include: (1) provision of biosecurity by limiting spread of diseases between cages and from the cage to the environment; (2) very low accumulation of ammonia and CO_2 within cages, allowing for a longer interval between cage changes of at least 2 weeks; (3) a decrease in

Table 1.3. Temperature and relative humidity (RH) guidelines.

Species	United States Department of Agriculture Animal Welfare Act (USDA AWA)	Institute for Laboratory Animal Research (ILAR) Guide	Canadian Council on Animal Care (CCAC) Guidelines
Rabbits	Not specified	30–70% RH, 61–72 °F (16–22 °C)	40–70% RH, 16–22 °C
Guinea Pigs	60–85 °F	30–70% RH, 68–79 °F (20–26 °C)	40–70% RH, 18–22 °C
Hamsters	60–85 °F	30–70% RH, 68–79 °F (20–26 °C)	40–70% RH, 21–24 °C
Gerbils	Not specified	30–70% RH, 68–79 °F (20–26 °C)	40–70% RH, 15–24 °C
Chinchillas	Not specified	Not specified	Not specified
Mice	Not covered	30–70% RH, 68–79 °F (20–26 °C)	40–60% RH, 20–26 °C
Rats	Not covered	30–70% RH, 68–79 °F (20–26 °C)	40–60% RH, 20–26 °C

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rodent allergens in the macroenvironment, with concomitant benefits to personnel; and (4) provision of protection of personnel and other animals from pathogens, that is, biosafety improvements.

IVC have also permitted increased use of rodents that are immunodeficient because of genetics or experimental manipulations, providing a protected environment for animals that could otherwise succumb to opportunistic infections. IVC do reduce intercage communication of mice and may create drafts for animals because of high air exchange rates, leading to reports of decreased breeding performance in some lines of mice. There is also discussion of the optimal cage change interval for IVCs in that cages may remain dry for extended periods because of the high air flow rates, but animals may be housed largely on dried feces with insufficient substrate. Intracage ammonia levels can be too high if cage change intervals are too long. Alternative systems that permit communication of animals between cages as well as reducing exposure of personnel to potential laboratory animal allergens (LAA) are ventilated cabinets with interior racks for caging.

Health Maintenance

Facilities and caging should be cleaned and sanitized when necessary, usually one to three bedding changes per week for mice, rats, guinea pigs, chinchillas, and rabbits, and longer intervals (up to biweekly) for hamsters, gerbils, and rodents held in individually ventilated cages (IVC). Ammonia gas, which increases susceptibility to respiratory tract disease, can be reduced by decreasing population density, use of IVC (to a limit), and by providing good sanitation and frequent bedding changes. In general, pelleted cellulose bedding is superior to wood or corncob for absorbing urine and lowering ammonia levels in cages. Bedding substrate and nesting material should be provided in a sufficient volume to permit digging, nest-building, and thermoregulatory choice. Vermin must be excluded from animal housing areas, as feral rats and mice may be a source of parasitic, viral, and bacterial pathogens. Different species and animals with unknown or non-SPF disease status should be housed separately, preferably in different rooms or in IVC. Professional and technical personnel or companion animal owners should examine animals at least daily for evidence of injury and disease. Stock and replacement animals should be obtained from reputable dealers or pet animal suppliers. Many animals in the pet trade are infected with one or more pathogenic organisms, and the stress and consequences of transport, marginal nutrition, mixing of species and sources of animals, inbreeding, and suboptimal environmental conditions may exacerbate underlying disease conditions.

Nutrition

Food should be stored in closed containers, kept at room temperature or below, and observed regularly for mold or vermin. Feeding and watering devices should be kept clean, be designed or placed so as to prevent fecal and urine contamination, be appropriate for the species and age of animal housed, and be accessible and functional. The shape of the animal's face may determine whether it can access feed and water devices, and this issue should be given close attention. Water should be fresh, clean, and available ad libitum and at all times. Specially designed watering bags with reusable valves are manufactured for use in laboratory animal facilities, and may provide ergonomic and labor benefits in certain circumstances while still providing continuous access to potable water. Gel-based diets ("gel cups") are frequently used when shipping rabbits and small rodents for extended distances, and also may be used to provide fluid and nutritional support for debilitated animals, animals recovering from surgery, or those adjusting to a new environment (Figure 1.6).

Rabbits and rodents should be fed a fresh, clean, nutritious, palatable feed on a regular basis and in an adequate quantity. Diets milled for laboratory animals typically include a milling date and should be used within 6 months of manufacture. Diets available for companion rodents are highly variable, and seed-based diets should be avoided in lieu of a pelleted chow manufactured by a reputable company for the specific species being fed. Discounted, outdated, or improperly formulated feeds, supplements, and vitamin formulations should be avoided. Colorful, attractive displays of rodent and rabbit feeds in pet stores should be scrutinized closely. The most common deficiencies encountered in pet store rabbit and rodent feeds are low protein content (under 16% crude protein), excessively long storage with subsequent nutrient decomposition, and inappropriate species use, particularly for guinea pigs, which require daily vitamin C in the diet. Smaller bags of food purchased more frequently are likely to provide more nutrients and vitamins to pets than large quantities of food that will take months to consume. Supplementation with grains, salt blocks, and vitamins is typically unnecessary

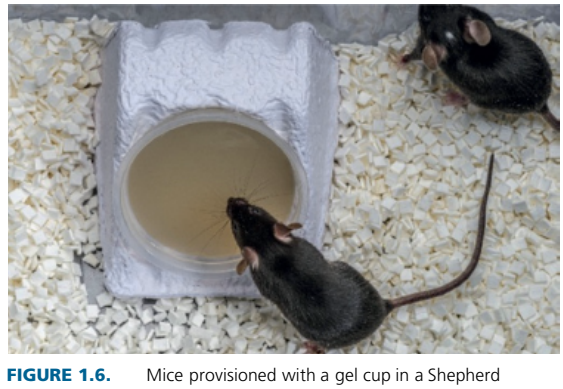


FIGURE 1.6. Mice provisioned with a gel cup in a Shepherd Shack®, providing both a shelter and ensuring successful acclimation of mice after shipping to a new facility. Courtesy of Shepherd Specialty Papers®.

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if the diet is properly formulated. Treats, such as fresh fruits and vegetables, may be used to reinforce desired behaviors, but should never consist of more than 5–10% of the daily diet. Clean timothy or other grass-based hay is available prepackaged and should be provided ad libitum for pet rabbits, guinea pigs, and chinchillas. Many mice and rats will also consume and use hay when it is provided. Similarly, sterilized or gamma-irradiated timothy hay can be provided to research rabbits and rodents to promote gut health and reduce boredom. Free-choice hay is not commonly provided to meat rabbits because it reduces feed efficiency and slows animal growth, but some hay is helpful to improve gut health, maintain normal wearing of their teeth, reduce enteric disease, and reduce boredom and development of abnormal or stereotypic behaviors.

Although the nutritional requirements of rabbits and rodents have been investigated and reported, optimal nutrient levels for most species remain uncertain. Requirements known at present are available from feed company publications or from the publications of the US National Academy of Sciences' NRC. With the important exception of ascorbic acid deficiency in guinea pigs and caloric, water, and protein deficiencies in all species, malnutrition is uncommon in rabbits and rodents. Primary nutritional imbalances may be manifested as weight loss or failure to gain, increased susceptibility to disease, hair loss, poor hair coat, prenatal mortality, agalactia, infertility, anemia, deformed bones, central nervous system abnormalities, or a reluctance to move. Subclinical nutritional deficiencies, excesses or imbalances may contribute to secondary infections or metabolic disorders.

The most prevalent nutritional problem in companion rabbits and rodents, and in laboratory animals held long-term, tends to be obesity associated with ad libitum feeding of high-calorie foodstuffs, including treats, and insufficient dietary fiber. More specific information about nutritional requirements and nutritional-related diseases for each species, and for companion versus laboratory animals, is provided in Chapter 2.

Identification

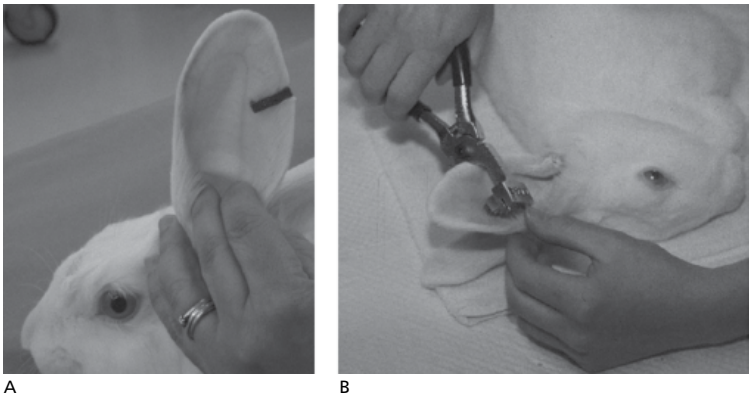
Animals worked with in research settings should be clearly identified using accepted methods—preferably those that are minimally invasive. Animals may be identified by cage cards, individual coat pattern, ear punch or notch, shaving hair patches, nontoxic marker or dye-staining on light colored fur or skin areas, (mice, rats, and hamsters), ear tag or stud, or tattooing, for example, ear, tail, footpad or shaved flank (Figures 1.7–1.9).

Microchip devices that store animal identification information in association with physical parameters such as temperature are used in some research facilities and for some small mammal companions. An example of an ear notch/punch code is shown in Figure 1.10. This method can be used for individually identifying the animal as well as for collection of tissue for DNA genotyping.

Cage cards with information specific to the animal and protocol are required in research settings, and use of bar codes on cards can assist with electronic census tracking. Permanent individual animal identification is often used together with



FIGURE 1.7. Example of instrument used for ear punching of mice. Note that the tissue obtained from the hole punch can also be used for subsequent genotype analysis.



A B

FIGURE 1.8. A: Ear tag in a rabbit, B: Rabbit sedated and positioned for ear tattoo identification. Courtesy of Ernest Olfert.

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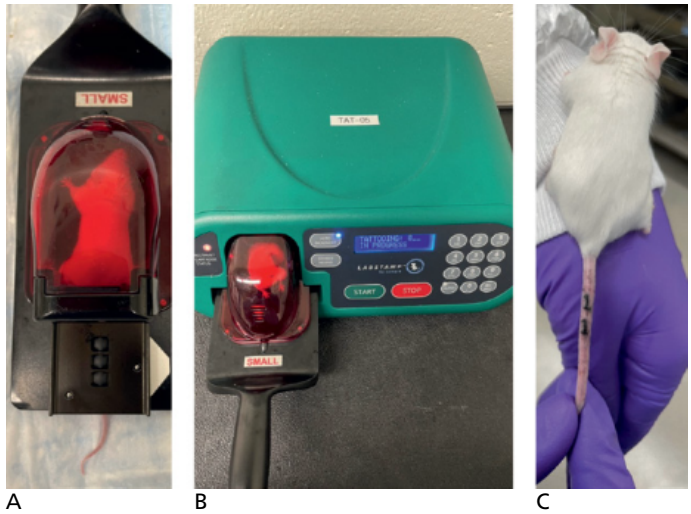


FIGURE 1.9. Tail tattoo in mouse. A: Mouse in tattoo cassette, B: Cassette inserted into tattoo device, C: Completed tail tattoo. Courtesy of S. Perrotta.

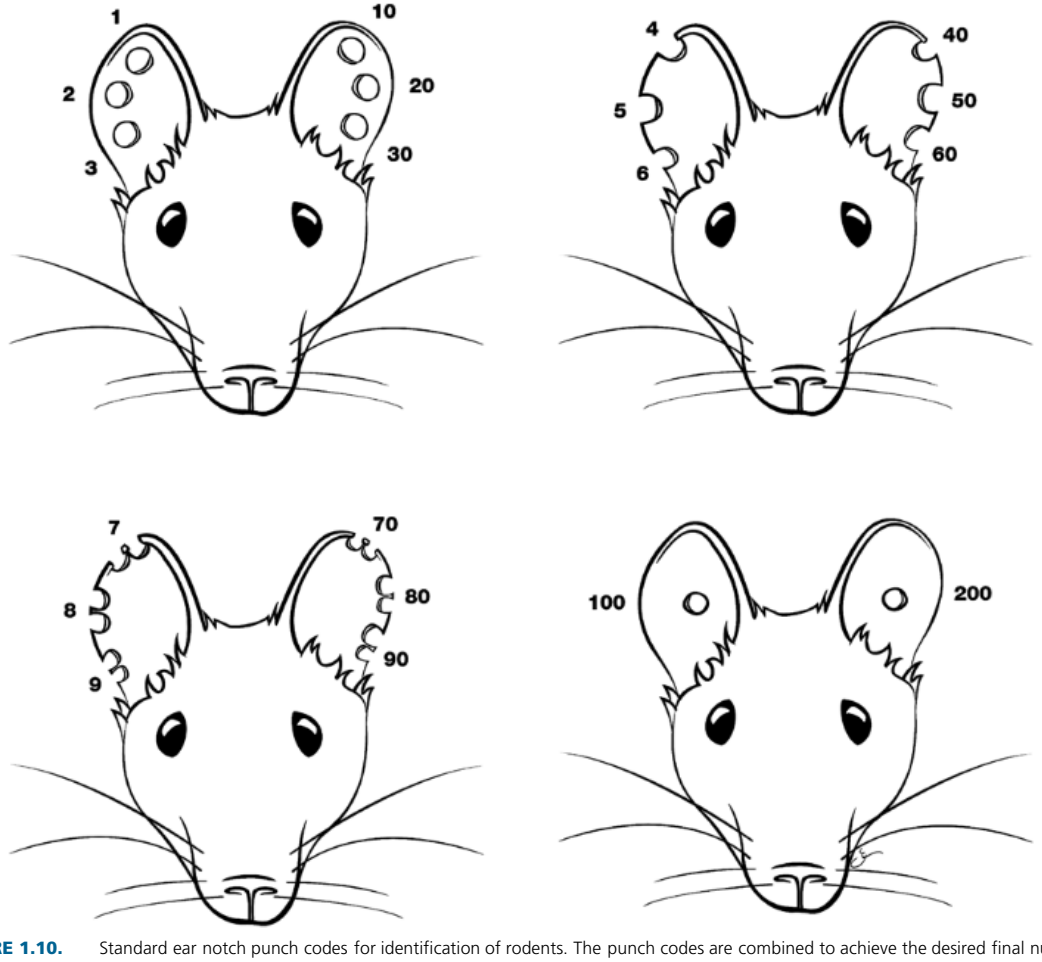


FIGURE 1.10. Standard ear notch punch codes for identification of rodents. The punch codes are combined to achieve the desired final number. Illustrations by Gianni A. Chiappetta.

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cage cards since cards can be inadvertently mixed during cage cleaning and experimental manipulations.

FACTORS PREDISPOSING TO DISEASE

Certain organic or environmental factors increase the exposure or reduce the resistance of animals to disease. These factors must be considered by animal caregivers in disease prevention efforts. Factors that influence disease susceptibility include environmental, genetic, metabolic, experimental, and dietary variables. Attention to these factors is extremely important in rabbit and rodent husbandry as well as in disease prevention and control. Many aspects of husbandry are mandated or discussed in detail in regulations governing the care and use of laboratory animals, and provide suitable guidelines for companion and production animals.

Facility Cleaning, Disinfection, and Fumigation

Good sanitation and hygiene are essential in rabbit and rodent maintenance. Very high levels of sanitation are required in an SPF research colony that may contain animals with immunodeficiencies or those infected with certain pathogens on an experimental basis. This level may not be necessary for companion animal and production facilities, but can be used as a basis for animal care. Clean cages are particularly important during pregnancy, lactation, and weaning; after removal of sick animals; after surgical procedures; and preceding the introduction of new animals into the household or colony. Some species (including hamsters, some strains of mice, and primiparous animals of all species) are better left undisturbed immediately following parturition, as disturbances may affect maternal care.

Cages can be disinfected by washing with 82 °C (180 °F) water after removal of organic matter or by applying a disinfectant solution to all surfaces. Disinfectant wipes or solutions, for example, hydrogen peroxide, phenolic, quaternary ammonium or halogen-containing compounds, including hypochlorite or dilute bleach solutions, are available in grocery, farm supply or feed stores, or from specialty manufacturers. Label instructions for concentrated solutions should be carefully followed for best results. Clients are more likely to follow advice about disinfection if common household products, such as bleach, vinegar, or common disinfectant wipes, are recommended. Detergents and disinfectants must be rinsed thoroughly from cleaned cages and feeders, as residues may cause serious health effects and may alter experimental data. Research facilities typically use specifically designed cage wash equipment and detergents to facilitate consistent sanitation of cages, feeders, and water bottles. Companion animal food bowls and water bottles can often be sanitized in home dishwashers. If items are hand washed, kitchen dishcloths should never be shared between human and animal dishes to prevent transmission of potential zoonotic infectious agents between animals and their human caregivers.

Disinfectants should be selected for broad spectrum activity, rapid kill effect, cleaning capacity, solubility, stability, residual activity, and lack of odor and toxicity. Ideally, disinfectants should be effective in the presence of organic materials, detergents, hard water, at varying pH levels, and on porous, rough, or cracked surfaces. Some disinfectant preparations should be avoided because they cloud clear plastic cages or cage accessories. Unfortunately, no single disinfectant meets all these criteria, and selection must be based on specific requirements. The effects of disinfectants vary with time of exposure, temperature and concentration of solution, and ionic content of the diluent. Important categories of microorganisms that are weakly or unaffected by standard disinfectant solutions are bacterial spores, coccidial oocysts, parasite ova, prions, and nonenveloped viruses. *Pseudomonas* spp. can be more resistant to disinfection than other bacteria and frequently contaminate watering devices, necessitating careful disinfection of this equipment. Use of acidified water to decrease *Pseudomonas* spp. burden is described in the mouse husbandry section of Chapter 2. All of these agents can induce topical irritation, burns, eye injury, if inadvertently splashed into the eyes, and respiratory irritation, in animals and people, and they should be used following manufacturer's safety instructions in well-ventilated areas. Agents should never be combined.

Halogen-containing disinfectants, including hypochlorites and iodophores, are effective in acidic solutions, but they may stain or damage fabrics and have reduced activity in the presence of organic matter, soap, or detergent residues. A good, practical, and safe disinfectant for pet or food animal cages is a solution of 30 mL of a 5% sodium hypochlorite solution (laundry bleach) in one liter of water (1 oz. per quart). A fresh mixture should be prepared just prior to use and used on clean cages or equipment only, followed by thorough rinsing and allowing time for items to dry.

Phenol derivative compounds, the disinfectants least affected by environmental influences, kill the vegetative forms of most Gram-positive and Gram-negative bacteria after approximately 30 minutes of contact time, and they can be found in some cold sterilant solutions. One exception is *Pseudomonas* spp., which require longer exposures and higher concentrations. Germicidal activity is increased with increased concentration and temperature of the solution. Phenolic compounds, emulsified at 1–5% in weakly acidic, soapy water, have some antifungal, sporicidal, and virucidal activity. Phenolics are also found in many common disinfecting antiviral wipes. Because of a residual odor and potential toxicity, phenolic derivatives should not be used to disinfect feeders and waterers.

Quaternary ammonium compounds are effective against Gram-positive bacteria, and many fungi and viruses, but are considerably less effective in the presence of organic matter,

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soaps, and an acidic pH. These compounds are useful for general purpose disinfection and for cleaning feeders and waterers, though as mentioned previously, devices should be thoroughly rinsed afterward. Residues of these compounds have been shown to impair reproductive performance in mice and have been implicated as a cause of death among suckling rabbits. Other disinfecting substances used less often and for resistant organisms such as bacterial spores, parvoviruses, parasitic ova, and coccidial oocysts include oxidizing disinfectants, formalin/formaldehyde, and ethylene oxide gas. Ammonia solutions are effective cleaning agents but are not typically effective against viruses.

The alkaline urine of rabbits, guinea pigs, and hamsters (above pH 8.0) contains phosphate and carbonate crystals that result in scale residues on caging. Acidic products, for example, dilute inorganic acids including white vinegar, can be used to dislodge the crystal accumulation. Some plastics are affected by alkaline detergents, which cause the transparent plastic cages to become cloudy and brittle. Acid detergent preparations are less destructive, but they will discolor aluminum.

Gas fumigation is an effective method for room and cage sanitization and for eliminating parasites and vegetative bacterial forms following removal of organic matter. Before gas fumigation is attempted, the room must be free of animals and people, airtight, warmed to at least 21 °C (70 °F), and wetted to raise the relative humidity to 80% or more. Vaporized hydrogen peroxide is used increasingly because it is noncorrosive, less toxic to people and animals, it requires minimal postprocess neutralization, and it produces ecologically friendly nontoxic waste products (water and oxygen). Formaldehyde gas has been used for fumigation for years and is generated by heating paraformaldehyde crystals in an alkaline solution on a hot plate. Chlorine dioxide or peracetic acid can also be used for fumigation. Because of the potential for severe toxicity with these alternative agents, provisions must be made for exhausting fumes from the room without the entry of personnel, and stainless steel and other equipment that may be corroded by fumigants should be removed before fumigation.

New methods of sterilization and newer chemical sterilants have been developed in response to emergence of antibiotic-resistant organisms present in hospital settings. These include new aldehydes, acids, and surfactant agents.

ALLERGIES TO RABBITS AND RODENTS

The high prevalence of allergies to laboratory animals (LAA) has been recognized for decades, and has been reported in 11–44% of people with repeated unprotected exposures to rabbits and rodents. This issue has not been widely discussed or evaluated in small mammal pet owners or among meat rabbit producers or rabbit abattoir workers. It is likely that exposure in a research animal setting under circumstances of repeated and frequent exposures to large numbers of animals, their dander, and their excreta contributes to the high prevalence of this health condition. The allergic reactions among people in frequent contact with animals involve both contact (dermal and ocular allergic dermatitis and conjunctivitis) (Figure 1.11) and inhalant (respiratory allergic rhinitis, bronchial hypersensitivity) syndromes. LAA may progress to asthma in up to 22% of affected persons and can result in anaphylaxis in severely allergic persons. The generation of immunoglobulin E (IgE) against antigens produced by laboratory animals is a prerequisite for diagnosis of LAA. Specific clinical signs include runny and itchy eyes and nose, a persistent cough, asthma or shortness of breath, or various skin manifestations, including wheal and flare reactions, hives, and pruritic rashes (urticaria). Sensitivity reactions may occur immediately, 15–20 minutes after exposure or many hours later. It is difficult to be in contact with animals without having contact with allergens, as even very small quantities of allergens can trigger a reaction. Allergens have also been detected on clothing and in the cars and offices of people who have had animal contact in other areas.



FIGURE 1.11. Generalized wheal-and-flare reaction on the arm of an individual with laboratory mouse contact allergies.

Predisposing factors for development of allergies to animal allergens unrelated to occupational exposures include atopy (clinical hypersensitivity of hereditary predisposition) and smoking. The intensity, frequency, and directness of contact are the most important associations related to development of LAA. Allergies are usually species-specific, that is, particular to one species of animal or another, but not strain-specific. Development of one allergy increases the probability that allergies to additional antigens may occur. Development of LAA has been recorded in association with exposures to rats, guinea pigs, rabbits, mice, hamsters, and gerbils; virtually any laboratory animal can induce allergies in exposed and predisposed individuals. The most difficult allergies to manage are those to rats and mice, but this likely reflects the fact that the numbers of these animals are greatest in most research animal

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facilities. Many mouse and rat urinary proteins belong to a family called lipocalins. These proteins resemble antigens of schistosomes, which are human trematodes (flukes). These proteins are highly prone to triggering IgE production, which likely accounts in part for the high proportion of the population susceptible to LAA. Three distinct mouse allergens and two allergens of rats have been described and are found in hair, dander, urine, and serum. Allergens have not been as well characterized in other species, though at least two lipocalin-like proteins have been identified in rabbits and guinea pigs, and are present in urine, saliva, and dander.

Various animal factors influence the risk of exposure to LAA and examples of these follow. Female mice generate far fewer airborne allergens than do males. Airborne prealbumin and albumin are reduced when corncob bedding is used in place of wood shavings. Rabbit saliva is deposited on the fur during grooming. After drying, the allergens become airborne and serve as an important source of exposure. Allergens in aerosolized rat urine can be carried with ammonia gas. These exposures may be particularly dangerous because they can be associated with severe pulmonary congestion. Symptoms develop rapidly after sensitized persons enter rat facilities that have poor ventilation and infrequent cage cleaning. Proteinuria in rats increases with age; consequently, exposure to these animals puts people at higher risk for allergy development.

This discussion clearly illustrates that laboratory animal facilities should have occupational health programs in place that consider development of LAA as a risk of employment, and employees with predisposing factors should be identified and monitored periodically as part of the program. The need for occupational health awareness is well described in the ILAR Guide, and ILAR has also published a volume titled *Occupational Health and Safety in the Care and Use of Research Animals* to provide additional information on this topic. Veterinarians or owners with small mammal pets or production animals should be aware of the possibility of development of allergies, and should seek the advice of a physician if they believe they have an allergy to rabbits or rodents.

Prevention

Rabbit and rodent airborne allergens and particulates can be measured, allowing for association between environmental exposures and development of LAA. This technology has also allowed evaluation of husbandry methods that decrease ambient concentrations of airborne allergens. These studies are the basis for recommendations for reduced occupational exposures. Because nonoccupational risks can increase the risk of development of LAA, many laboratory animal facilities include a preemployment risk assessment as part of their occupational health program.

An effective LAA prevention program includes education and training; implementation of personal protective equipment (PPE), including gloves, designated work clothes, or laboratory coats, and respiratory protection; modification of work practices; and most importantly, use of various engineering controls to reduce the level of allergen exposures. Use of ventilated cages that are pressurized negative to the room and that are opened only in ventilated changing stations reduces mouse allergens 10-fold relative to nonventilated caging handled on conventional change tables. Increasing room ventilation rates and humidity, use of low-dust bedding, wetting bedding prior to dumping, use of ventilated dump stations, and using room-level air filtration are all measures that decrease allergen exposures.

Persons experiencing allergic symptoms with exposure to laboratory animals should be evaluated by a physician with experience in allergy diagnosis and management. Diagnostic tests that may be performed include skin tests or in vitro assays that detect IgE reactions to LAA. Pulmonary function measurements may be used to assess asthmatic symptoms. Possible management for sensitized individuals includes reduction of exposure, pharmacologic treatment, or immunotherapy. Early intervention is essential, as prognosis for control of symptoms and overall outcome is highly dependent upon disease severity at the time of diagnosis.

Small mammal pet owners can minimize allergen exposure by keeping the animals in well-ventilated areas, providing regular sanitation of cages and the surrounding environment to reduce allergen levels, using dust-free bedding, and ensuring appropriate hand and clothing hygiene after handling these pets. On farm, ensuring adequate ventilation is essential for reducing environmental allergens.

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Meat and Fur Production

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https://www.extension.iastate.edu/4h/rabbit—Iowa State University. Extension services rabbits.
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Chapter 2

Biology and Husbandry

Chapter 2 covers selected topics on the biology and husbandry of rabbits, guinea pigs, chinchillas, hamsters, gerbils, mice, and rats. The sections are divided into 11 categories: origin and description, anatomic and physiologic characteristics, the animal as a companion animal, housing, feeding and watering, reproduction, disease prevention, public health concerns, uses in research, biodata, and sources of information. The references listed in each section may be found in university and public libraries or ordered from bookstores or publishers. Relevant websites deemed to have reliable and current information as of this edition (2025) are also listed. Further information about the seven species included in this chapter is given, often in considerable detail, in the general reference works listed in Chapter 1.



THE RABBIT

The domestic or European rabbit can be a companion or show animal, raised for meat, wool, or byproducts, or a research subject. Companion rabbit popularity has significantly increased in recent years, and, consequently, so has the body of knowledge contributing to our understanding of individual rabbit husbandry and disease. If rabbits are raised in appropriately resourced and constructed enclosures; receive adequate water and a suitable diet; and are protected from predators, drafts and temperature extremes, obesity, and subclinical infections, they will grow rapidly, reproduce well, and live healthy lives.

Origin and Description

Rabbits and hares are lagomorphs in the family Leporidae. The other lagomorph family, Ochitonidae, consists of a few typically high-altitude-dwelling species known as pika. The domestic rabbit, *Oryctolagus cuniculus*, is descended from the wild rabbits of Europe and northwestern Africa, where wild *Oryctolagus* still exist. Rabbits have been at least semi-domesticated for nearly 200 years. Domestic rabbits have become feral in some areas of the world, most notably Australia. Wild rabbits are gregarious, burrowing, herbivorous, crepuscular animals related distantly to rodents and diverging from them in the Paleocene epoch (55–65 million years ago). Size, shape, and color variations, derived from centuries of selective breeding, define over 50 breeds that are recognized by the American Rabbit Breeders Association (ARBA). Representatives of the large breeds (6.4–7.3 kg or 14–16 lb) are the giant chinchilla and the Flemish giant. Among the medium-sized breeds (1.8–6.4 kg or 4–14 lb) are the California and New Zealand white rabbits. Small breeds (0.9–1.8 kg or 2–4 lb) include the Dutch and Polish breeds (see Figure 2.1 for breed examples).

The albino New Zealand white is popular for meat production and research, rex and angora breeds are bred for their fine hair and pelts, and the smaller breeds are typically found as companions, show, and research animals. Companion or house rabbits are often crosses of different breeds. Optimal husbandry and medical practices may vary among breeds, sources, sizes, and environments, and recommendations appropriate for colonies of New Zealand white rabbits, for example, may not be suitable for home-raised, individual pet rabbits that are litter-box-trained. Production rabbits require yet other considerations unique to their purpose.

O. cuniculus is the only genus of European or domestic rabbit. Hares (*Lepus*) and cottontails (*Sylvilagus*) are in different genera. Hares and rabbits are named inconsistently, for example, the jackrabbit is really a hare and the Belgian hare is a rabbit. Rabbits are born naked and helpless (altricial), whereas hares are born furred and with their eyes open (precocious). Fertile, cross-genera matings do not occur due to different chromosome numbers (*Oryctolagus* spp. has 44 chromosomes while *Lepus* spp. has 48 chromosomes). Orphaned young hares and cottontails are kept occasionally as pets, but inhalation pneumonia, injury, and death are common consequences of attempts at hand rearing infant animals. Long-term care of orphaned rabbit kits is best left to well-established wildlife rescue organizations.

Anatomic and Physiologic Characteristics

Rabbits have a well-developed nictitating membrane or third eyelid. During sleep or anesthesia this membrane moves from the medial canthus across the cornea. Rabbits have a wide field of vision that reaches 190° for each eyeball. Their significant pupillary dilatation results in a light sensitivity approximately eight times that of humans. Rabbits possess a double retinal system of rods and cones, and their eyes readily detect motion and are very sensitive to the blues and greens present

Harkness and Wagner's: Biology and Medicine of Rabbits and Rodents, Sixth Edition. Patricia V. Turner, Colette L. Wheler, Hugues Beaufrère, Niora Fabian, and John E. Harkness.
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A



B



C



D



E



F

FIGURE 2.1. Typical appearance of several rabbit breeds, A: Dutch, B: Rex. courtesy of G. & R. Grambo, C: French lop. courtesy of G. & R. Grambo, D: Angora. courtesy of M. Johnston, E: Chinchilla. courtesy of M. Johnston, F: Jersey wooly. courtesy of M. Johnston, G: Lion head. courtesy of M. Johnston, and H: Netherland dwarf. courtesy of M. Johnston.

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G

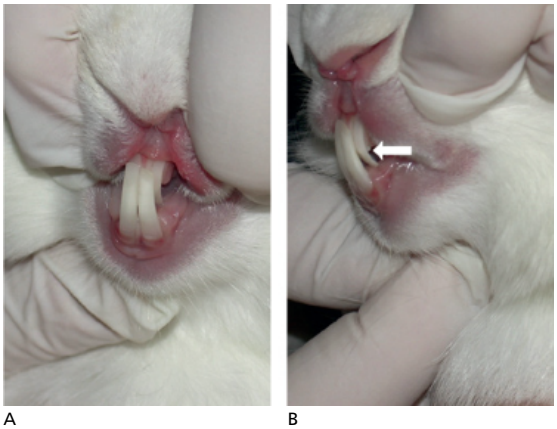


H

FIGURE 2.1. (*continued*)



FIGURE 2.2. Normal rabbit incisors. Note the relative lengths of the maxillary and mandibular incisors.



A B

FIGURE 2.3. Rabbit incisor malocclusion. A. Frontal view. B. Side view (arrow points to peg tooth).

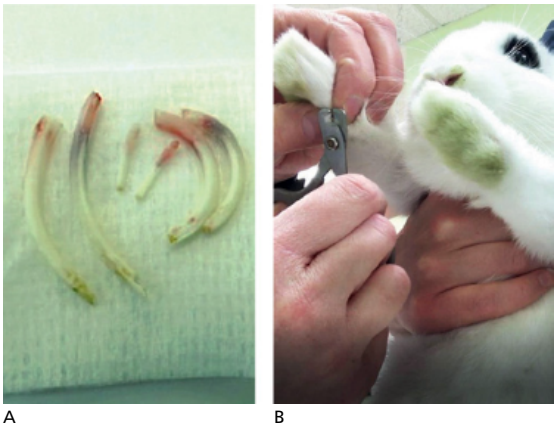
at twilight. These ocular characteristics facilitate recognition of predators via visual cues. Rabbits cannot see below the horizon, however, and use their sensitive vibrissae and lips to find forage. Rabbit ears are highly vascular organs that function in heat regulation, sound gathering, and as convenient sites for intravenous injections and blood sampling. This site might not be advisable for all breeds nor all materials to be injected, as perivascular injections of irritating substances may result in sloughing of the ear margins or tips. The ears are fragile and sensitive and should not be used for restraint.

Rabbit teeth are open rooted (continuously growing) (Figure 2.2). On each side of the mouth there are 2/1 incisors, 0/0 canines, 3/2 premolars, and 3/3 molars. Lagomorphs have a second pair of incisors ("peg teeth") in the upper jaw, one feature that classifies them into *Lagomorpha* versus *Rodentia*. Peg teeth protect the palate from trauma from lower incisors (Figures 2.3 and 2.4).

Malocclusion and dental overgrowth occur most often with incisors, which grow an average of 10–12 cm (4–4.8 in) per year throughout the rabbit's life. Peg teeth may overgrow also, as can the premolars and molars (cheek teeth). Malocclusion may result from either or both congenital anomalies in jaw and tooth formation and inadequate fiber and roughage in the diet (Figures 2.3 and 2.4).

The thoracic cavity is small compared with the capacious abdominal cavity, and this is important to remember when rabbits are positioned on their backs for surgery, as the intestinal weight on the diaphragm may interfere with normal chest excursions during breathing. The intestine is approximately 10 times the body length and includes a large cecum and glandular

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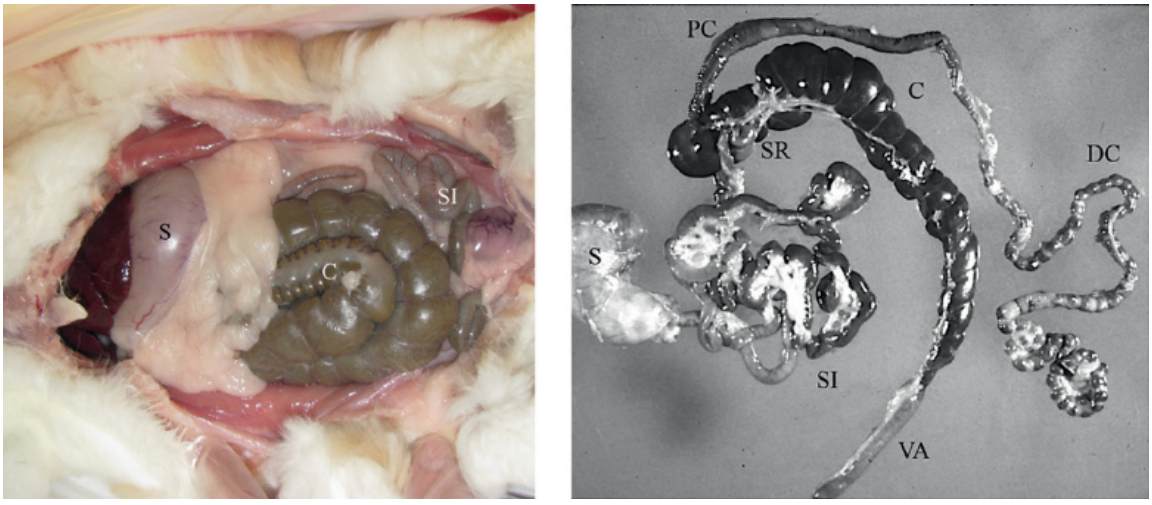
A B

FIGURE 2.4. A. Rabbit incisors following extraction. From left to right, pairs represent: upper, peg, and lower incisors. B. Nails also must be examined and trimmed regularly as part of overall rabbit care. Courtesy of Calgary Avian and Exotic Pet Clinic.

stomach. The vermiform appendix at the free end of the cecum and sacculus rotundus (the pale fleshy tissue at the ileocecal junction) are prominent lymphoid organs associated with the rabbit's intestine (Figure 2.5). The fragile skeleton comprises only 8% of the animal's body weight, compared to the cat's skeleton, which comprises 13% of its body weight. The long bones and lumbar spine, encased in relatively large muscle masses, are susceptible to fracture, particularly in young animals with incomplete growth plate calcification. The rabbit has a comparatively small heart, and the right atrioventricular valve may be bicuspid or tricuspid. Rabbits have delicate, thin-walled veins that tear easily, and they have a very narrow linea alba. The inguinal canals, leading to the inguinal pouches (scrotal sacs), remain open for the life of the rabbit. The testes descend at 12 weeks but are capable of abdominal retraction throughout the animal's life. Females have a separate cervix for each uterine horn. Rabbits have 8–10 mammary glands, arranged in broad bands from the throat to the groin that are only visible in the mature female. Rabbit milk is high in fat and protein compared with other mammals.

Rabbits have a soft dense undercoat and thin skin, making clipping fur difficult but contributing to the versatility of the pelt. Rabbits do not have footpads but instead have coarse fur on the plantar and palmar surface of the tarsus and carpus, respectively, where they contact the ground. Cage flooring should be constructed of solid or perforated metal or plastic or polished wire or plastic grid or slats to avoid damage to the feet, otherwise severe pododermatitis can develop.

The rabbit neutrophil, especially when observed in suppurative lesions, resembles an eosinophil because of the numerous intracytoplasmic eosinophilic granules. These cells are more appropriately termed heterophils because of their staining characteristics, but they have the same functions as neutrophils in other species. Heterophils (neutrophils) and lymphocytes are present in an approximate ratio of 1 : 2, respectively, except during certain infections, when the ratio may reverse. Basophils are more common in rabbits (2–10% in differential white blood cell counts) than in other mammals. The composition of proteolytic and mucolytic enzymes in heterophils of the rabbit



A B

FIGURE 2.5. Normal gastrointestinal anatomy of the rabbit in situ (A) and dissected (B). S, stomach; SI, small intestine; SR, sacculus rotundus; C, cecum; VA, vermiform appendix; PC, proximal colon; DC, distal colon. A—courtesy of Calgary Avian and Exotic Pet Clinic. B—courtesy of D.H. Percy. Reprinted with permission from Blackwell Publishing.

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results in production of viscous suppurative exudates characteristically observed during bacterial infections.

Rabbits as Companion Animals

Behavior

Rabbits make good companions and are generally quiet and clean animals. They can be litter box trained, particularly if they are neutered. Rabbits groom themselves meticulously, and animals with unkempt hair coats should be examined closely for signs of ill health. Rabbits have several recognizable vocalizations. A purring sound is made when they are generally content, and grunting or growling indicates displeasure or territoriality. Bruxism (tooth grinding) is a sign of pain or discomfort, and loud squealing occurs when they are in significant pain or in a highly fearful situation. Rabbits will also thump a hind foot as an isolated response to aversive (fearful or painful) situations. When given sufficient space for exercise, rabbits will perform hops, jumps, random leaps and twists in the air ("binkies") and may run around the space in a burst of speed ("zoomies"). When relaxing, rabbits will often flop on their sides. Rabbits will scent mark objects and people by rubbing with their chins ("chinning"), and they will nudge objects with their noses during exploration. While some rabbits may enjoy sitting on or near their caregiver not all enjoy being petted. They are inquisitive and curious animals that enjoy exploring their surroundings. Rabbits like to dig and chew and must be supervised closely when they are outside of their home enclosure as well as in the presence of other companion animals, such as cats or dogs. Rabbits are readily trained using positive reinforcement techniques, which can enhance bonding with their human caregiver and provide cognitive stimulation for the rabbit.

Some rabbits may nip lightly when young, and this can be discouraged by consistently making a loud noise when this occurs (e.g., saying "ouch" in a high-pitched voice). Older bucks and primiparous does with strong territorial instincts may vigorously defend their enclosures and may rush at and bite people when they reach into the animal's cage. These rabbits should be allowed to exit the enclosure on their own, where they can be handled in neutral territory. Aside from this, biting is uncommon unless a protruding finger is mistaken by the rabbit as a food item. Rabbits can, if improperly restrained or if naturally aggressive, inflict substantial scratches with their powerful rear limbs. Rabbits protect themselves through acute senses, burrowing, agonistic displays, and thumping of the rear feet in response to perceived aggression. Otherwise, agonistic behavior is confined to the breeding cage, where pursuit, tail flagging, urination, squealing, and combat are exhibited. Aggressive behavior varies among breeds, with Dutch belted being more aggressive than New Zealand whites and lops, in that order. Sexually maturing rabbits (older than 3 months) may attack one another, require multiple hiding places in their enclosure, and they may need to be housed separately (Figures 2.6 and 2.7). Wounding, pseudopregnancy, and infertility may occur in group-housed does, unless groups are established before sexual activity begins or animals are neutered as juveniles and gradually introduced to one another (Figure 2.8). Introductions of new animals should be gradual and supervised, and it is imperative to provide sufficient space and shelters or visual hides for rabbits to escape agonistic behavior during this process. Mature and intact rabbits of the opposite sex should be paired only at mating and separated afterward. It is recommended that companion rabbits be neutered to decrease aggression, increase compatibility for social housing, and improve litter box behavior.



FIGURE 2.6. Group-housed mature rabbits (intact and neutered does and neutered bucks) at rabbit rescue facility. Important housing components include multiple nesting places, shelters, and food and water bowls to reduce competition. Courtesy of M.Cant.

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FIGURE 2.7. Male rabbit with scrotal wound and exposure of testis following fight with another male rabbit.



FIGURE 2.8. Pair-housed female New Zealand white rabbits. Pairing success can be enhanced by ensuring litter mates are kept together during transport and after receipt at the research facility. Courtesy of K.A. Mooney.

Life Span

A medium-sized rabbit has a breeding life from approximately 4.5 months to 3–4 years of age, an average life span of 5–6 years, and a possible longevity of 15 years. In general, dwarf breeds will live longer and reach sexual maturity earlier than larger breeds.

The breeding life of a doe may consist of 7–25 litters before the number of young per litter (7–8 for medium breeds) declines, although it is unusual for breeding does to exceed 2 years of age and breeding bucks to exceed 3 years of age in commercial settings. In hobbyist settings, breeding senescence in does may be caused by progressive endometrial fibrosis and subsequent failure of ova to be implanted.

Handling and Restraint

Rabbits readily habituate to gentle handling, but may become tense or struggle when handled in novel surroundings or by new people, as may occur in a clinic or research setting. To carry a rabbit a short distance, the neck skin is grasped with one hand and the rear quarters supported with the other with the entire body held firmly against that of the handler for security ("football" hold) (Figure 2.9); alternatively, a small rabbit can be grasped over the back. Grasping the rabbit under the thorax and supporting the rump so that the rabbit assumes a "C"-shape position ("cradle" hold) is a method that allows examination of the ventrum. Another method involves stretching the rabbit and holding its dorsum snug against the body (upright hold). To carry animals longer distances, a secure, lidded box or carrier is recommended. Alternatively, the rabbit can be placed on the bearer's forearm with its head concealed in the bend of the elbow, while the opposite forearm presses the animal securely against the holder's body. Commercial plastic restraint devices are also available (Figure 2.10).

Covering the animal's eyes with a towel may help to allay fear and struggling. When rabbits are handled improperly, they may struggle vigorously and break their backs or scratch the handler. Wrapping a rabbit snugly in a towel or blanket ("towel wrap"; see Figure 2.11) may help to alleviate anxiety, prevent struggling, and facilitate examination or transportation of the animal for short distances.

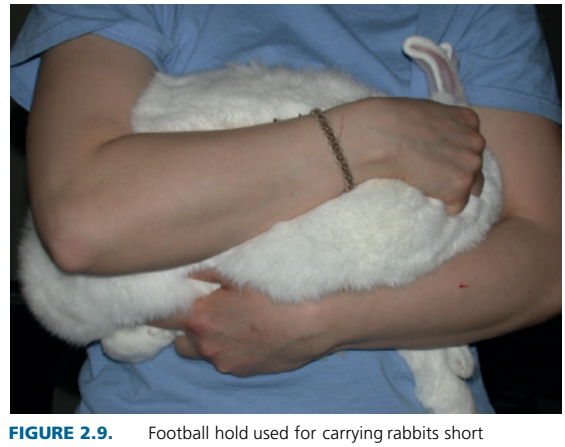


FIGURE 2.9. Football hold used for carrying rabbits short distances. The rabbit's face is tucked under the handler's elbow to minimize visual stimulation, and rabbit's hind end is controlled by the handler's opposite forearm and elbow.

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A


B


C

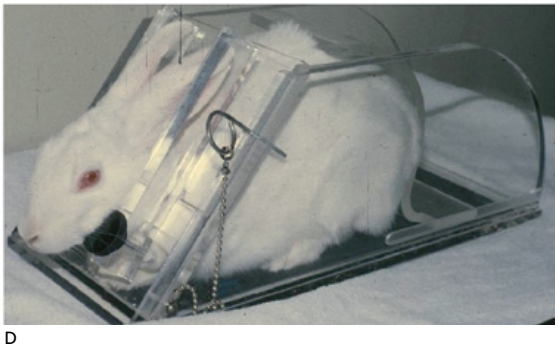

D

FIGURE 2.10. Alternate methods for rabbit restraint, A: cradle hold for small rabbits. courtesy of M. Johnston, B: upright body hold, C: table hold for injection, with hand's pressing over the pelvic and pectoral limbs to prevent bolting and D: plastic commercial rabbit restrainer. courtesy of E.D. Olfert.

Rabbits should never be lifted or restrained by their ears. Similarly, grasping the loose skin over the back too tightly during restraint is painful and may lead to subcutaneous bruising (Figure 2.12). Rabbits are stressed when held on their backs. As a prey species, rabbits have evolved various tactics to help them avoid predation. One of these is called "tonic immobility"—sometimes referred to as "trancing" or "hypnotizing." Some research suggests that rabbits in this position experience a near-death experience, and it is associated with changes in cardiac rate and function, respiratory rate, and increased corticosterone levels. Therefore, tonic immobility should not be used for rabbit handling or restraint.

Housing

Plans for outdoor rabbit hutches are freely available online or from libraries and feed companies. Assembled wire cages, with ancillary equipment, are available from farm-supply stores, pet stores, or mail-order houses that advertise in publications of rabbit breeder associations or at conventions. Caging is also advertised in professional and trade publications.

In Canada, the National Farm Animal Care Council has published a Code of Practice that details requirements for ensuring proper housing and care of farmed meat rabbits. The European Food Safety Authority (EFSA) has also published

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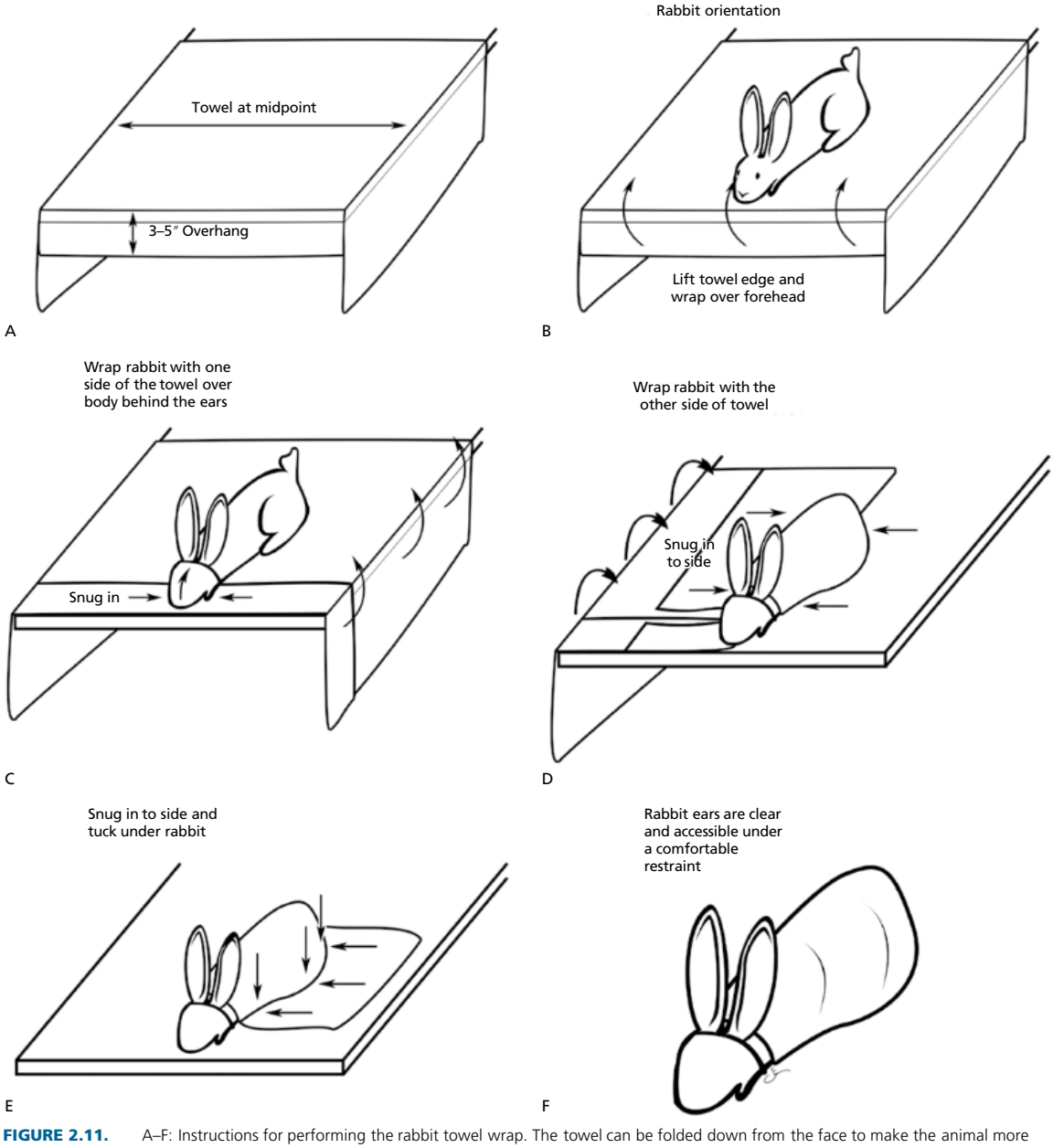


FIGURE 2.11. A–F: Instructions for performing the rabbit towel wrap. The towel can be folded down from the face to make the animal more comfortable for longer periods of restraint or for face mask induction for anesthesia. Illustrations by G. Chiappetta. Bottom image demonstrates final wrapped rabbit.

guidance on health and welfare considerations for farmed rabbits kept under different production systems. EFSA acknowledges that while some organic meat rabbit farms use outdoor housing, because of the variability in housing quality and the protections offered to rabbits, the welfare of meat rabbits is generally better when they are kept indoors. While intact male bucks used for breeding are always housed singly, there is increasing interest in housing breeding does as small groups of 2–3 animals before and after parturition in elevated parks or pens. In this housing paradigm, breeding does are shut out from group housing from approximately 8 days prior to parturition to 18 days after parturition. While there may be some initial scuffling and chasing while does establish a hierarchy, fighting is minimal when barriers are re-opened at 18 days

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FIGURE 2.11. (*continued*)



FIGURE 2.12. Meat rabbit carcass demonstrating acute subcutaneous bruising acquired just prior to slaughter and attributed to handling.

post parturition. After weaning, fattening kits are group-reared in parks or pens until sent to market.

Critical considerations when designing or purchasing rabbit housing include the purpose of the animal (i.e., companion, laboratory, or production); structural strength of housing materials; absence of sharp edges and rough surfaces; adequate size, space, and resources, or other furnishings to permit some choice and control in the environment including resting, exploration, and ability to escape or isolate from conspecifics including kits for breeding does (e.g., through the use of platforms, shelters, or elevated shelves that animals can sit on top of or hide underneath); thermal comfort; provision of some solid flooring or a resting mat for comfort; ease of cleaning; protection from climate extremes; corrosion resistance; and provision of appropriate numbers and types of waterers and feeders for the numbers of animals to be housed. Companion and research rabbits are frequently housed in large floor pens, crates, or cages made of stainless steel and/or high-density plastic with perforated solid bottoms and litter substrate, such as wood shavings or straw (Figures 2.13–2.17). Trays are often built-in under suspended rabbit caging into which large pieces of absorbent paper are placed to collect urine and feces that fall through the floors. This helps to reduce ammonia and keep rabbits clean and dry.

Rabbits should be housed in areas that are commensurate with the animal's use, size, and weight, and in accordance with current regulations or guidelines (Table 2.1). Recommendations for companion rabbits vary, but have been suggested as enough floor space for three hops and tall enough to accommodate an animal standing on its hind legs ("periscoping") without their ears touching the top of the cage. It is also suggested that if rabbits are confined to a hutch or cage during the day, they should be provided with supervised exercise at least several times weekly. In addition to relieving boredom and allowing rabbits to work out pent-up energy, this helps to maintain adequate bone density, which minimize the risk of leg and back fractures.



A



B

FIGURE 2.13. A: Typical suspended wire housing used for commercial rabbit operations. B: Well-padded nest box with kits from commercial meat rabbit cage. Both courtesy of K. Keels.

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FIGURE 2.14. Stainless steel cage exercise for laboratory rabbit housing. Multiple levels encourage movement of paired rabbits, a litter box with substrate is provided for digging and resting, and hay is provided free choice. Courtesy of S. Authier.

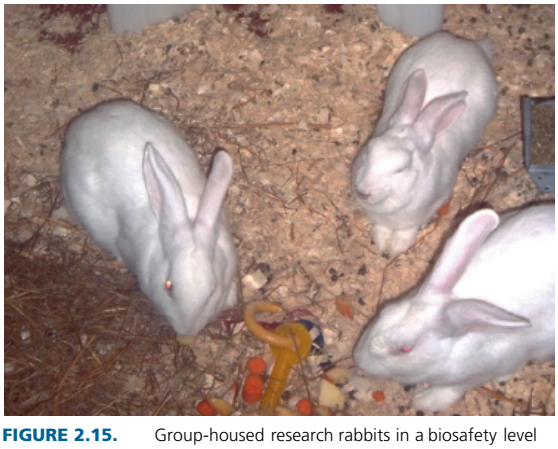


FIGURE 2.15. Group-housed research rabbits in a biosafety level 2 infectious disease study. Rabbits are provided with free choice hay and food items for foraging in addition to areas for hiding. Animals are comforted by each other's presence and choose to rest together. A fourth rabbit is resting out of sight in the pen.

Other considerations for keeping rabbits include providing resources for foraging and for animals to chew and manipulate. Wild rabbits spend a considerable amount of awake time seeking food, and providing hay or other low-calorie, high-fiber treats to domestic rabbits in novel and interesting ways helps to prevent boredom. Chew toys, aspen or hardwood blocks or sticks, and other devices should be constructed of nontoxic and nonsplintering materials and require periodic cleaning and rotation to ensure engagement. Broken and highly chewed objects should be removed and replaced to minimize injuries. Large cardboard tunnels or empty feed or bedding bags make good hiding places for rabbits and are destructible and engaging for them.



FIGURE 2.16. Two companion rabbits housed comfortably in a floor pen. Nonslip flooring is provided by indoor–outdoor carpet, the pen contains several litter boxes, and a hiding place is available. Courtesy of C. McMahon.



FIGURE 2.17. Pair-housed mature pregnant does. Housing has elevated resting area and surfaces are made from more comfortable thermoneutral materials. Courtesy of W. Archibald.

In general, rabbits are social species and benefit from being housed with one or more other rabbits. The key to successfully co-housing rabbits is to provide sufficient space and shelters or visual hides to allow rabbits to move out of the line of sight of other rabbits, when needed. Intact, young-to-mature sibling does or neutered bucks may be housed together with few problems (Figure 2.18). Unfamiliar neutered rabbits can be introduced to each other, but it may take time for them to habituate to each other's presence. Animals should be supervised closely to disrupt fighting during pair or group establishment. Once dominance hierarchies are established aggression will usually diminish. Intact male rabbits are typically separated at weaning or no later than 12 weeks of age, whereas mature, intact does used for breeding can be housed in same-sex pairs or small

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Table 2.1. Minimum cage size requirements for rabbits used in biomedical research in the United States and Canada.

Rabbit size	Floor space/animal[a] ILAR guide[b]	CCAC guide[c]
Up to 2 kg (4.4 lb)	0.14 m^2 (1.5 ft^2)	0.37 m^2
2–4 kg (4.4–8.8 lb)	0.28 m^2 (3 ft^2)	
4–5.4 kg (8.8–11.9 lb)	0.37 m^2 (4 ft^2)	0.47 m^2
>5.4 kg (>11.9 lb)	0.46 m^2 (5 ft^2)	
Doe with litter	Additional 0.19 m^2 (2 ft^2)	0.93 m^2

[a] Based on current Institute for Laboratory Animal Research (ILAR) Guide for the Care and Use of Laboratory Animals (2011) and the CCAC's Guide to the Care and Use of Experimental Animals, vol. 1 (1993).
[b] Minimum cage height 0.45 m (16 in).
[c] Minimum cage height 0.4 m (15.6 in) for animals up to 4 kg and 0.45 m (17.6 in) for animals >4 kg.



FIGURE 2.18. Floor-housed juvenile research rabbits. Courtesy of W. Archibald.

groups from approximately 12 weeks of age. In research settings rabbits can readily be pair or group housed by means of cages with adjoining doors or through the use of floor pens. Ideally, research rabbits housed in cages should be given regular access to an exercise pen under supervision (Figure 2.19).

Rabbits are generally housed indoors at temperatures between 4 °C and 29 °C (40–85 °F), with a recommended average between 16 °C and 21 °C (61–70 °F). Rabbit cages should not be placed in direct sunlight, to avoid overheating of animals. Lower environmental temperatures are tolerated well, and rabbits may be housed safely outside provided they are sheltered from wind and drafts, protected from predation and insect vermin, and kept warm and dry. In hot weather (above 29 °C or 85 °F), outdoor hutches or cages should be cooled by ventilation, shade, evaporator pads, or overhead sprinklers (with the latter, care must be taken to prevent excessive wetting of rabbits).



FIGURE 2.19. Exercise pen for cage-housed female laboratory rabbits composed of plastic polymer with deep wood shavings provided as substrate. Rabbits spend out-of-cage time with other rabbits in the same experimental group several times weekly. Courtesy of W. Archibald.

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Other characteristics of the rabbit's environment should include a moderate relative humidity (30–70%), adequate draft-free ventilation, regular removal of droppings and tray paper, and a daily cycle of 14–16 hours light for females and 8–10 hours light for males, often compromised as 12 : 12 hour light–dark cycles. Shortening of daylight hours may depress sexual activity, as may occur in the shortening days of autumn. Although hanging wire cages may remain superficially clean for weeks, hair and matted feces accumulate, requiring regular sanitation. The feet of rabbits can become excessively soiled when there is poor drainage or removal of urine and feces from the floor of their pen or cage. This can contribute to the development of pododermatitis, ulceration, discomfort, and pain, and foot hygiene should be monitored routinely. A scoring system can be used to assess home cage hygiene in adult rabbits (Figure 2.20).

Rabbits use a preferred latrine area in their cage for defecation and urination (see Figures 2.6 and 2.16), which makes house training possible. Litter-trained rabbits may still soil outside the litter box on occasion. Pans for droppings should be emptied, and enclosed hutches should be cleaned weekly or more often, as needed. Flies are attracted to rabbit droppings, and hatched fly larvae or maggots may give the false impression that the rabbits have "worms" on their hind quarters. Flystrike can have serious consequences for rabbit health and is an indication of a need for improved husbandry. Properly ventilated and dried manure troughs in production facilities can be left undisturbed for months. However, cleaning of rabbit cages to remove feces, debris, and fomites that may contain infectious agents is particularly important before parturition, during weaning, before installing new stock, and after removing a sick animal. Laboratory rabbit cages are sanitized with chemicals, steam, or a combination of these methods at intervals not exceeding every 2 weeks.

Due to their herbivorous diet, rabbit urine has a pH of approximately 8.2, which results in crystallization of minerals and turbid crystalluria. Rabbit urine varies in color from light yellow to deep orange or red brown because of porphyrin accumulation, and color is enhanced by dehydration and alkalinity. This may be mistaken for hematuria by owners. The carbonate and phosphate salt scale that accumulates on cage surfaces is difficult to remove, and requires soaking in acids prior to washing for adequate descaling.

Detergents, disinfectants, and lime-scale removers can be applied with a stiff brush in routine cage cleaning. Acidic solutions damage floors and metals with prolonged contact, and should be used cautiously and rinsed thoroughly. Sodium hypochlorite (5%) or household bleach mixed at 30 mL per liter of water (1 oz/quart) is an excellent disinfectant for small animal caging but should be left in contact for at least 10 minutes before rinsing. Flaming may be necessary to remove hair and kill coccidial oocysts and may be used for disinfection of meat rabbit production facilities. Absorbent compressed cellulose or wood chip is recommended as a substrate to line a house rabbit litter box, and the box is best spot cleaned on a daily basis with a complete change once every 1–2 weeks, depending on the type of litter used. Dilute vinegar can be used to remove scale. Clay or clumping litters should not be used in a rabbit litter box.

Breeding bucks should be protected from high temperatures to avoid periods of sterility. At temperatures of 29 °C (85 °F) and above, especially in heavily furred older rabbits in high humidity, heat stress may lead to sudden death or infertility. Does may experience embryonic mortality under similar conditions. High temperatures reduce feed intake and increase water consumption, whereas cold increases both, if the water remains unfrozen.

Feeding and Watering

Rabbits are monogastric, hindgut-fermenting herbivores. They prefer low-fiber, high-protein, high-carbohydrate portions of plants, which are usually the tender, succulent

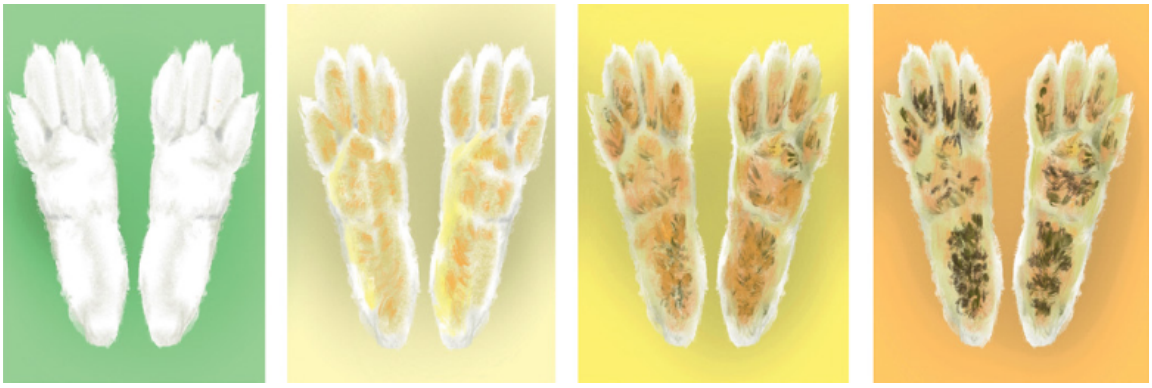


FIGURE 2.20. Foot hygiene scoring system for rabbits, with scores ranging from A (normal, clean) to B (lightly soiled) to C (moderately soiled) to D (heavily soiled, wet and dirty). Modified with permission from Masthoff and Hoy (2019). Illustrations by K. Sokolowski.

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portions; however, offering too many young, fresh greens can be detrimental to their health. Some microbial digestion of cellulose occurs in the rabbit large intestine. The microflora also ferments ingesta, producing digestion products essential to nutrition, including amino acids, volatile fatty acids, B complex vitamins, and vitamin K. The rabbit utilizes these end-products by direct absorption across the mucosa or following cecotrophy (=coprophagia), in which cecal contents are re-ingested as cecotropes. Rabbits eat various forages, including leaves, grass, weeds, and other plant byproducts. They digest 70–80% of forage protein, which makes them among the most efficient users of plant protein.

Consequences of good nutrition in medium-sized production rabbits are gains of 30–40 g (1–1.4 oz)/day to a weight of 1.8–2.3 kg (4–5 lb) by 8–10 weeks; up to 11 litters of 7–8 young annually; and an absence of diet-related disease. Adult male rabbits eat 110–175 g (4–6 oz) of pellets/day; pregnant does eat 175–225 g (6–8 oz)/day; lactating does eat 225–450 g (8–16 oz)/day; rabbits 3–6 weeks of age eat 50–75 g (1.7–2.5 oz)/day; and rabbits 6–8 weeks of age eat 125–150 g (4–5 oz)/day. Rabbits begin eating dry feed at 16–18 days of age. Consumption varies with ambient temperature, water availability, and other factors. Diets high in starch and carbohydrates lead to a multitude of gastrointestinal and systemic diseases. Progressive production rabbit facilities provide high-fiber, low-energy diets to fattening rabbits ("fryers"), and a higher energy ration to breeding animals. Because of the capacity of rabbits to convert low-quality feed efficiently, rabbits are an important food source not only for wild predator species but also for human populations. The meat is also low in cholesterol and fat, compared to muscle from other animals, such as chicken, beef, or pork.

Rabbits naturally exhibit coprophagy, usually in the early morning, and ingest large quantities of protein- and vitamin-rich mucin-covered feces (cecotropes) directly from the anus. This soft, moist, mucus-covered "night stool" is swallowed whole and may be seen in the stomachs of dead rabbits. Juvenile animals will consume cecotropes from the dam, which helps to populate their gastrointestinal tract with a mature microflora (Figure 2.21). Wire floors do not inhibit coprophagy.



FIGURE 2.21. Coprophagy is a normal activity of a rabbit in which cecotropes are ingested directly from the anus. In this image, two juvenile rabbits are seen to consume cecotropes produced by their dam. Courtesy of M. Huynh. Inset: Cecotropes produced by adult rabbit. Courtesy of Calgary Avian and Exotic Pet Clinic.

Food Consumption

Rabbits are fastidious eaters and may reject otherwise acceptable foods because of odor, texture, form, or method of presentation. Rabbits eat to satisfy a specific caloric requirement. Under conditions of lower ambient temperatures, food consumption increases, which may lead to excessive protein consumption and secondary renal problems. Thus, lower-protein diets may be considered for winter feeding if rabbits are housed outside. At higher ambient temperatures, consumption decreases. In cold weather, dwarf rabbit breeds and does of any breed at peak lactation may not consume adequate calories and may develop a negative energy balance. Does with litters of more than five kits may require more rations, while does with smaller litters should be limit fed.

Rabbits prefer sweet foods, but despite this preference, high-calorie foods should be avoided. High-fiber, low-energy diets transit the gut rapidly, allowing increased intake both to satisfy caloric requirements and to fill the digestive tract. Cecotrope production is also reduced with low-fiber diets because of hindgut hypomotility. Hypomotility may lead to gastric stasis as well as either or both diarrhea and cecal impaction.

Rabbits prefer pelleted diets of medium diameter (around 5 mm × 12 mm, or 0.2 in × 0.5 in) with bentonite clay as a binder. Food intake peaks at mid-pregnancy and 2–3 weeks into lactation; intake decreases around kindling and around weaning (30 days postpartum). Restricting feed of fattening rabbits may improve food energy conversion without impairing weight gain. Restricting intake of energy-rich food to the doe postpartum (then gradually increasing) and to young animals postweaning may reduce undigested starch reaching the cecum and potential carbohydrate fermentation with secondary gut dysbiosis and diarrhea. Restricting intake also reduces abdominal fat deposits and rate of hair growth cycle, both characteristics that improve pelt quality and ease of removal. Research rabbits are commonly moderately feed restricted prior to shipping to reduce the impact of stress-associated gastrointestinal stasis. Pelleted feed should be gradually increased over 2–3 days to normal levels once rabbits arrive at their destination, whereas grass hay can be fed ad libitum before, during, and after transportation. Depending upon the distance being shipped, some feed pellets and hay can be added to shipping crates to give animals something to chew and eat while in transit. Water in the form of gel packs

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can also be provided. Ideally, rabbits should be habituated to the gel pack before shipping.

Supplementation of a small daily amount (2–3 oz, 60–90 g) of pelleted high-fiber diet composed of timothy or prairie grasses, with ad libitum feeding of quality grass hay (high fiber, low calcium, for example, timothy or brome grass hay) is common. This type of diet has had noted success in reducing obesity, gastrointestinal stasis, urolithiasis, various enteropathies, dental disorders, and hair chewing. In addition to relieving boredom, offering hay daily helps to keep teeth worn, reducing the risk of dental disease. Rabbits chew soft foods and pellets versus grass or long strands of hay differently. Hay and grass are initially apprehended by the lips and bitten off by the incisors and then chewed using a side-to-side motion, a pattern not seen when softer foods are consumed. Grass hay (e.g., timothy, brome, Kentucky bluegrass, rye) are high in fiber and silicates and low in protein. The silicates in grass hay help to wear down the cheek teeth crowns of rabbits, preventing malocclusion. Alfalfa hay is a more digestible legume-type of forage that is high in calcium and protein and low in fiber. It does not provide the same beneficial effects for rabbit dental and gut health and quantities fed should be limited. Provision of salt, table scraps, vitamins, antimicrobials, and herbs without provision for a balanced diet is not advised. Fallen leaves and tree bark provide extremely low levels of nutrients and should not be considered as feed for domestic rabbits. Wild rabbits only consume these items when no other food sources are available. Rabbits can be given small quantities of fruits, carrots, and green leafy vegetables as treats, but these should never exceed 5–10% of the animal's daily intake and should not be fed to overweight animals. Habituating rabbits to these special foods or treats may be useful in young rabbits as they will be more inclined to eat them later in life as appetite stimulants, if they become sick.

Spinach, kale, and dandelion greens are all foods that are high in calcium and should only be fed in small amounts, on an intermittent basis, to minimize the potential for renal disease. Homemade nonpelleted diets are possible for neutered nonproduction rabbits, but the composition should be considered thoughtfully to avoid overfeeding of calcium-rich foods and to ensure that the diet is well balanced with sufficient levels of daily fiber, protein, trace minerals, and energy. Animals reared for meat production or for research are typically fed a commercial pelleted rabbit-specific diet balanced for fiber and protein, and supplemented with free choice grass hay and small quantities of other food treats.

Because the rabbit's intestinal microflora is sensitive to the intestinal milieu (e.g., osmolarity, pH, starch content), changes in diet, especially in the 4-to 12-week-old rabbit that is transitioning from a fat- and protein-rich milk-based diet to a diet high in fiber, should be gradually made over a 4- to 5-day period to allow adjustments in the balance of normal flora. Old and new feeds can be combined during this conversion period.

Intestinal Flora

The neonatal rabbit stomach has a pH of 5.0–6.5, which does not kill food microbes, but until 3 weeks of age, octanoic and decanoic fatty acids within the stomach keep microbial populations low. The higher stomach pH allows weanlings to acquire their adult gastrointestinal bacterial flora. Gastric acidity from weaning into adulthood has a pH of 1.0–2.0, which keeps the stomach and upper small intestine essentially free from resident bacteria. Facultative anaerobes (e.g., enterococci) colonize the large intestine early, followed by strict anaerobes, primarily Gram-negative *Bacteroides* spp. Spore-forming bacteria are present in smaller numbers, including low levels of several clostridial species. *Escherichia coli* may be present in low numbers, but lactobacilli are usually not present because of the lethal effects of low gastric acidity and bile acids and because they do not adhere to the intestinal mucosa. If the cecal substrate contains increased amounts of highly soluble carbohydrate, clostridial and coliform bacteria may proliferate or produce enterotoxins, dysbiosis, diarrhea, and death.

Gastrointestinal Function

The rabbit intestine eliminates fiber rapidly as hard, dry pellets, and efficiently breaks down nonfiber components. Eighty percent of ingesta reaches the cecum by 12 hours post ingestion. Rabbits chew thoroughly (120 times/minutes) and reduce pelleted feed to powder, although mucin-wrapped cecotrophs are swallowed whole.

Twenty-four hours after beginning a fast, the stomach may still be half full, partly because of coprophagy, and some content is still present 11 days into a fast. The small intestine functions as in other mammals. In the cecum and proximal colon, muscular, mechanical activity separates large particle insoluble fiber from soluble small particle carbohydrates and proteins. The insoluble fiber is passed through the haustrated (sacculated into small pouches) colon and forms the familiar hard fecal pellets. During chyme separation, an aldosterone-mediated, active uptake of fluid occurs into the lumen of the upper colon, the fusus coli. The fluid then passes with small fiber and other solutes by retrograde motion back into the cecum. Materials in this fluid undergo fermentation in the cecum and are packaged eventually by cecal and colonic action as soft cecotropes for consumption directly from the anus. Cecotropes have 26–29% protein and 14–18% fiber content, whereas dry fecal pellets have 9–15% protein and 28–30% fiber. Hard feces are passed for approximately 4 hours post-feeding and cecotropes for the next 4 hours. In the wild, rabbits usually eat at dusk; however, domesticated rabbits of all types prefer to eat numerous small meals throughout the day and night. Bacterial action (mostly by *Bacteroides* spp.) in the cecum produces volatile fatty acids (mostly butyric acid), B complex and K vitamins, and bacterial protein. Fatty acids are absorbed directly and are the major energy source for the hindgut, whereas vitamins and proteins are reprocessed after coprophagy. Heat treatment of feeds may alter starch and

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facilitate digestion. The lymphoid cecal appendix is rich in bicarbonate and may buffer cecal acids, or it may affect microbial fermentation in other ways.

Nutrient Requirements

Energy

The nutrient requirements of rabbits fed ad libitum are approximately 2,500 kcal/kg of diet during growth, gestation, or lactation, whereas maintenance requirements are 2,100 kcal/kg of diet. Growing and lactating rabbits, dwarf breeds, and rabbits in cold climates have higher caloric requirements. A once-daily feeding (limit feeding) of approximately 90–120 g (3–4 oz or 2/3 cup) of pellets can be used to maintain an adult medium-sized rabbit at a constant weight. Provision of free choice grass hay helps to occupy rabbits between feedings and can reduce destructive chewing of the environment as well as hair chewing. Use of self-feeding "J-shaped" hoppers are common in research settings and help to ensure that feed pellets remain clean.

Water

Rabbits drink a relatively large amount of water compared to other similarly sized mammals, and it is important that rabbits have a constant source of hydration. Rabbits consume twice as much water as food (weight basis) and the average daily water consumption is 120 mL/kg body weight (BW)/day. Water consumption increases dramatically with higher ambient temperatures, whereas food consumption over the same temperature change decreases from 184 to 125 g/day. Rabbits on high-fiber or high-protein diets drink more water to moisten and move food and to remove the urea load, respectively. Food deprivation and lactation requirements also increase consumption—lactation by as much as 10-fold. The 24-hour urine volume is approximately 130 mL/kg BW/day at pH 8. Although rabbits in production and research settings are generally provided with water in a bottle or via lixit for automated delivery, given the choice, rabbits prefer to consume their water via an open bowl, and this should be considered when providing water to companion rabbits. Sufficient hydration gel should be included in the crate when shipping rabbits between production sites and research facilities.

Fiber

Large-particle insoluble or lignin-containing fiber is not digested efficiently by rabbits and serves more to provide the bulk (i.e., pressure and irritation) needed for stimulating intestinal motility. Promotion of motility decreases diarrhea, which in the rabbit is typically associated with fermentation and hypomotility. In addition to the well-established protection against enteritis, fiber dilutes the energy content of a diet, prevents obesity, reduces hair accumulation in the stomach, improves dental health, and reduces hair chewing. Rabbit growth rate is optimal at 10–15% crude fiber, and diarrhea may result if the level decreases below 10%. A 15–17% dietary fiber level is adequate, and levels greater than 17% may retard weight gain, which may be desirable in sedentary adult rabbits. High-fiber (22.5%) diets are fed to reduce obesity and hair accumulation in the stomach. Roughages include timothy or other grass-based hay, rice hulls, grasses, and legume-based hay.

Protein

Rabbits efficiently digest plant protein, and obtain their amino acid requirements from simple forage and grain diets with about 10% of amino acids coming from cecotropes. Lysine and methionine levels are most likely to be marginal in rabbit feed. The optimal level of protein is 15–19%. Excessive protein levels not only increase feed costs, but also lead to high urea levels and ammonia formation with increased urine production and microenvironmental humidity. In addition, because of increased gastrointestinal pH, enteritis problems are increased. Protein sources include legumes (alfalfa, clover, peas, beans, peanuts), soybean and cottonseed meal, rapeseed meal, canola, sunflower seeds, fishmeal, and powdered milk. Soybean meal is highly palatable and highly digestible by rabbits, but is an expensive diet for production facilities.

Fermentable Carbohydrates

Carbohydrates (grain starch) provide much of the energy needed by the rabbit. High-energy diets contain approximately 3,200 kcal of metabolizable energy (ME)/kg feed, and lower-energy diets contain approximately 2,500 kcal ME/kg feed. A 1 kg production rabbit (6 weeks of age) requires 290 kcal/day, a 1.5 kg rabbit (7.5 weeks of age) needs 348 kcal/day, and a 2.0 kg rabbit (9 weeks of age) requires 423 kcal/day. At peak lactation, a doe needs three to four times maintenance levels, or 1,092 kcal/day, which cannot be met by ingesting conventional diets at maximum practical levels, especially diets high in added hay. A postpartum estrus 1–7 days after kindling is associated with a positive energy balance; from 10 to 28 days postpartum, does are energy deficient. Higher-energy lactation diets may be indicated (25% protein) in intensive breeding schemes. Low-fiber, high-energy, high-protein concentrates include cereal grains (corn, wheat, barley) and various milling byproducts: brans, middlings, mill runs, pulps, and tubers.

Minerals

The mineral needs of rabbits are met and exceeded easily because alfalfa and grain are often combined with limestone/calcium and a 0.5% trace mineral mix. Absorption of calcium from the gut is poorly regulated in rabbits compared with other mammalian species and appears to be independent of metabolic need or vitamin D level. Blood calcium levels are regulated through metabolism, and the relatively high plasma levels (3–4 mmol/L or 12–16 mg/dL), efficient renal excretion and reabsorption, and bone reabsorption of calcium are characteristics of domesticated rabbits. Alfalfa, the primary constituent of commercial rabbit pellets, is high in calcium and may underlie the high levels of serum calcium seen in many rabbits. The alkaline (pH 8) turbid urine is the primary route of calcium excretion for rabbits, whereas in other mammalian

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species, calcium is primarily eliminated in bile and feces. High calcium levels together with other physiologic or pathologic processes in rabbits may result in urolithiasis, red urine, or metastatic calcification and chronic renal disease, especially if excessive vitamin D is provided. As mentioned, dilution or replacement of higher calcium-containing alfalfa hay or alfalfa-based pellets with grass hay and pellets is advisable for companion rabbits that are not being bred intensively. A dietary ratio of calcium to phosphate of 1.5–2 : 1 is recommended. Lactating does have a higher requirement for calcium and phosphorus because of the very high mineral content of their milk. Adequate levels of other trace minerals, such as iron, cobalt, zinc, copper, manganese, and selenium are usually supplied as premixes in commercial rabbit diets.

Vitamins

Vitamin supplementation in rabbits is usually unnecessary because alfalfa and recycling of nutrients via coprophagy supply most vitamins. Rabbits convert 100% of beta-carotene in the diet to vitamin A, and the provisional requirement is met by a diet of 10,000 IU/kg. Sun-cured alfalfa has 50,000–150,000 IU/kg of vitamin A, and feed with 190,000 IU/kg of vitamin A can result in toxicity, including abortion, fetal resorption, small litters, hydrocephalus, and low survivability. Vitamin A deficiency produces similar signs. Low fetal uptake of vitamin A somewhat protects the fetus against overdose effects. The requirement for vitamin D is low because intestinal calcium absorption is efficient in the absence of vitamin D. Vitamin D toxicity does occur with levels higher than 2,300 IU/kg. Evidence of vitamin D intoxication includes emaciation, weakness, urolithiasis, renal disease, and widespread metastatic calcification. Vitamin E deficiency leads to infertility, abortions, still births, neonatal deaths, and muscular weakness. Vitamin E is generally added to the diet during production.

Reproduction

Sexing

Neonatal rabbits can be very difficult to sex; anogenital distance is the most reliable indicator (the distance being longer in males than females), but this may not be evident until animals are 10–20 days of age, and can be a problematic way to identify sex in a single-sex litter. The best policy for identifying the sex of a young rabbit is to recheck at 1 month of age if one is unsure. Males have a rounded, protruding penile sheath and os penis (baculum) with a rounded urethral opening, whereas females have an elongated vulva with a slit opening.

Stretching the perineum by lifting the tail (with the rabbit in sternal recumbency) provides a clear view of the anogenital structures and everts the penis from its sheath. The penis can be extruded at approximately 2 months of age. Paired, blind-ended perineal or inguinal pouches containing scent glands lie immediately lateral to the genital openings. These scent glands are used to mark kits and cage surfaces and may contain dried yellow-brown sebaceous material. In mature males, the hairless scrotal sacs are evident lateral and anterior to the penis. In immature males, the scrotal sacs are not readily apparent (Figures 2.22–2.24).

Breeding Stock Criteria

Many rabbit breeds exist, and obviously these breeds have specific phenotypic and genotypic criteria and breeding specifications, but the most popular rabbit breeds for meat and laboratory use are the New Zealand white and California breeds. Breeding

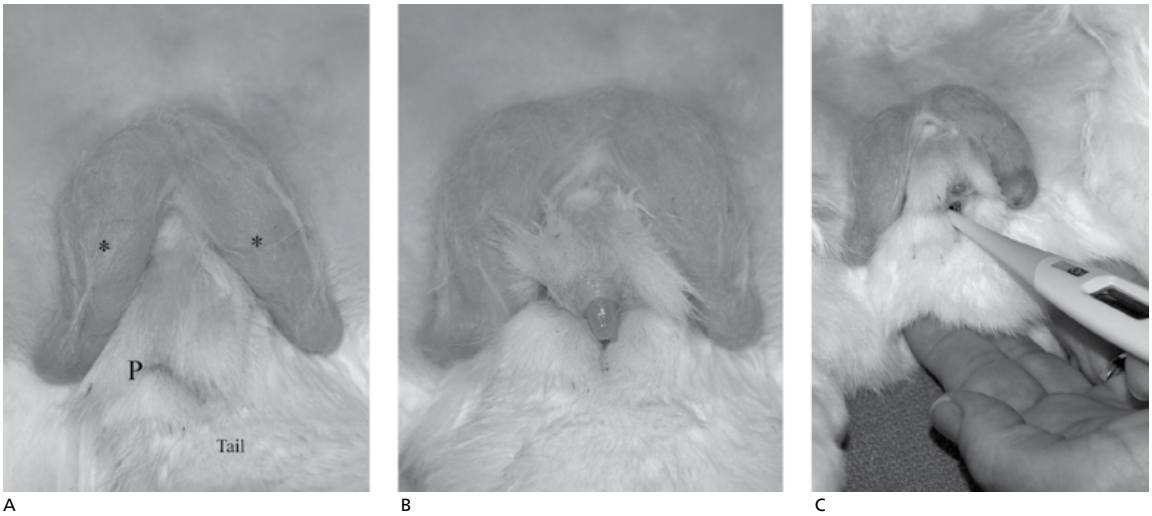


FIGURE 2.22. A. External genitalia of the male rabbit (P, penis; * denotes paired scrotal sacs). B. External genitalia of the male rabbit with the penis extruded. The penis overlies the anus. C. Anus exposed during insertion of thermometer for rectal temperature collection.

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FIGURE 2.23. External genitalia of the female rabbit. Only the urogenital orifices are visible as the tail must be retracted to see the anus.



FIGURE 2.24. Paired inguinal glands in a female rabbit (UG, urogenital orifice; G, inguinal gland). The tail is at the bottom of the picture. Note the close proximity of the anus and urogenital orifice. Care must be taken to insert the thermometer into the correct orifice when obtaining a rectal temperature.

stock may be selected for several criteria, but good health (*Pasteurella* and enteritis free) is essential. *Pasteurella*-free animals may be purchased from specific pathogen-free (SPF) vendors or high health commercial rabbit breeders, and are highly recommended for experimental research. SPF colonies are typically also free of hepatic coccidiosis, encephalitozoonosis, and *Bordetella* spp. Currently SPF New Zealand white and Dutch breeds are available from commercial vendors in North America. New Zealand white laboratory rabbits have been shown to suffer myriad health effects associated with *Pasteurella multocida* infection. The impact of pasteurellosis infection on other breeds of rabbits is less clear, and in most instances these animals are not selected as *Pasteurella*-free or SPF. Pasteurellosis contributes significantly to moribundity of production rabbits, and sneezing animals with nasal discharge should be culled regularly.

Moderately to highly heritable breeding characteristics of production rabbits include litter weight at 28 days and other characteristics related to growth and body weight. Traits of fertility and disease resistance have low heritability.

Other criteria for selection are consistent production of litters of 7–9 kits, a 570 g (19 oz) rabbit at 4 weeks and 1.8 kg (60 oz) rabbit at 8 weeks, dressing percentage of 57% or more, 10 teats, good mothering instincts, high feed conversion efficiencies, good coat condition, and good body conformation. Milk production in does is best determined by litter weight at 21 days. An important criterion for meat rabbits is total litter weight at market age (8–10 weeks), which should be approximately 12.5–15 kg. Criteria for culling from a production herd are two consecutive litters (not counting the first litter) with less than 7 kits or exceeding 12, high nest box mortality, poor maternal behavior, poor survival (under 60%) to weaning and marketing, aggression, fur chewing, excitement, and reluctance to mate (conception rate should be 70–85%). Criteria for selection of breeders for laboratory rabbits would also include screening for congenital defects, such as buphthalmia or brachygnathism; breed selection characteristics would include parameters such as coat quality and color.

Buck Criteria

Buck quality is extremely important in intensive production systems, as each buck may service up to two dozen does or more if artificial insemination (AI) breeding systems are used. Bucks should be selected to minimize inbreeding and should be kept lean and active during their breeding lives of 2–3 years. If used weekly or twice weekly, bucks should be limit-fed to prevent obesity. Selection of replacement bucks can be made as early as 21 days of age because, for males, weights at 21 days correlate well with weights at 56 days. Young bucks (5–6 months) should be placed with gentler does, because aggressive does may attack and permanently frighten the buck, ruining the animal as a breeder. Young bucks can be used two to three times per week, whereas mature bucks can be used once daily. Breeding bucks should be housed singly in cooler areas (less than 29 °C; 85 °F) of the facility but located conveniently near the does. For breeding, does are brought to the buck's cage and removed soon after breeding (usually within 5–10 minutes of pairing) to minimize opportunities for buck aggression. When conception rate and litter size decrease in a group of does, the buck should be culled. The buck should be free from disease because many diseases may be transmitted by direct contact or through semen when AI procedures are used.

Doe Criteria

Does are bred by age (4–6 months), by weight (3–4 kg), and by observation of congestion of the vulva, which indicates receptivity. Age at breeding depends upon size and breed and ranges

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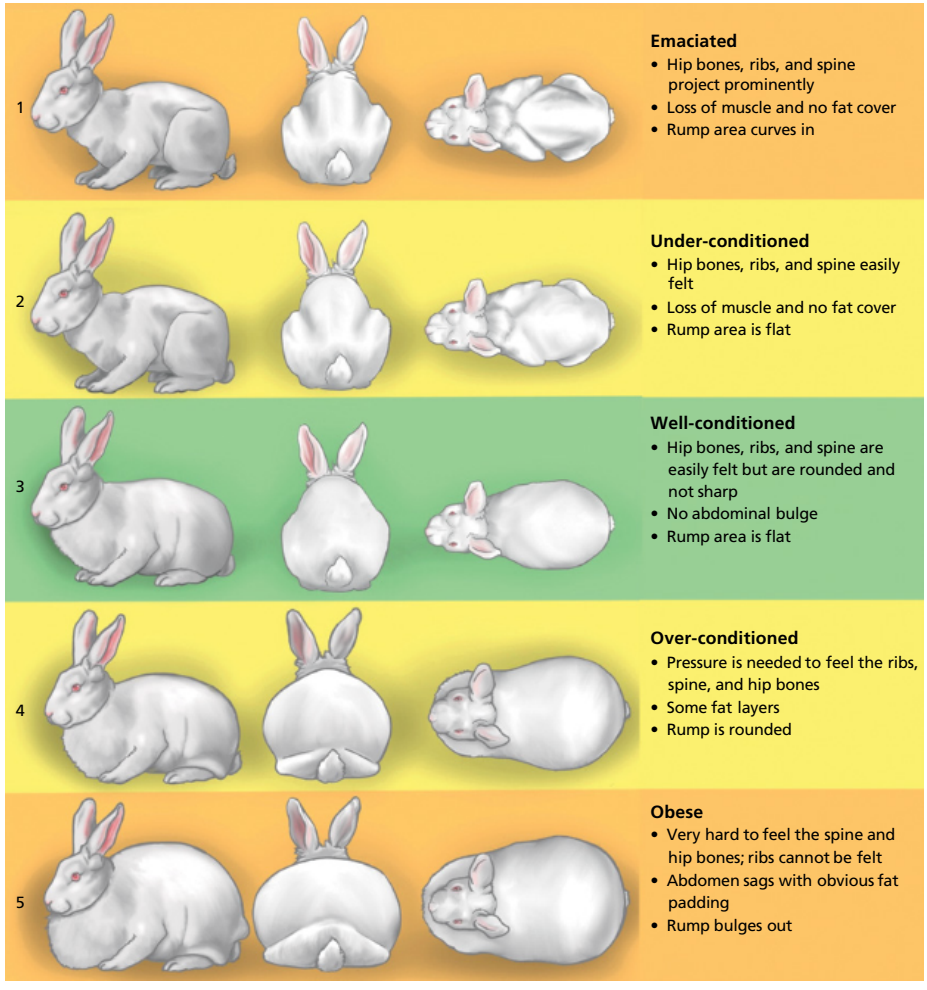


FIGURE 2.25. Body condition scores (BCS) for rabbits. Images depict scores between 1 (very thin) to 5 (obese). For the most accurate BCS estimate it is important to gently palpate the rabbit for bones and other structures noted in the descriptors, as a thick hair coat may hide bony projections. A BCS of three is optimal. Illustrations by K. Sokolowski.

from 4 to 5 months of age for small breeds to up to 9 months for large breeds. Management of the primiparous doe is important to ensure a long and healthy reproductive life. Young does should be in good body condition prior to breeding (see body condition scoring Figure 2.25). Healthy production does produce between 20 and 25 litters before litter size decreases, and in intensive breeding systems this number of litters can be produced in 2–3 years. One replacement doe and buck should be planned per month for every 12 does and 5 bucks in production.

Mating

Rabbits are induced ovulators and release ova 9–13 hours after copulation. Does do not have an estrous cycle, but they do have a 7- to 10-day period of receptivity followed by 1–2 days of inactivity during which a new wave of follicles replaces the atretic precursors. Receptivity is indicated variably by a swollen, reddened vulva, restlessness, chin rubbing, and standing and allowing mounting. Rabbits may be receptive during periods of pregnancy and lactation with libido peaks approximately 26 and 39 days postpartum. It is common to rebreed mature does in good body condition approximately 11 days postpartum. Ovarian activity, reflecting hypothalamic changes, is diminished as days shorten. The use of a 16 : 8 or 14 : 10 hours light : dark cycle, adequate caloric intake, and a slightly increased ambient temperature may prevent or reduce this suppressive seasonal and environmental effect.

Does are carried to the buck's cage; if mating is to occur, it will be evident usually within a few minutes of introduction.

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The pair together should be observed to ensure that at least two intromissions have occurred, and the doe should not be left unsupervised with the buck more than 30 minutes to decrease opportunities for savaging by the buck.

Artificial Insemination

Artificial insemination can be an economic and efficient method of breeding large numbers of does; however, skill and labor are required that may negate other advantages of the procedure. Semen from a single buck may be extended to fertilize 500 does. Semen is collected from a trained and experienced buck using an artificial vagina in the presence of a receptive teaser doe. Such collections may occur two to three times each week. After obtaining the 0.3–1.0 mL ejaculate, the gel plug is removed, and the semen is kept at 37 °C and used within 12 hours or diluted in egg yolk sodium-citrate extender.

To induce ovulation, gonadotropin-releasing hormone (GnRH; 10 µg) or luteinizing hormone (LH or human chorionic gonadotropin; 1.25 mg in physiologic saline) has been injected intramuscularly immediately following insemination; however, this involves extra expense as well as handling and injection of does. Increasingly, does are managed through increases in the photoperiod and, if she is still lactating, by closing the nest box access for up to 24 hours prior to planned insemination to increase ovarian follicular activity. For AI procedures, a doe is restrained on her back or held between the thighs of the operator sitting on a stool or held in a smooth restraint tube with the hind end and genital papilla facing upward (Figure 2.26); insemination is effected through a smooth, short, and flexible pipette inserted almost full length into the anterior vagina.

Breeding Schedules

The schedule or number of litters produced per year is determined by goal of production, that is, meat, show, research, or companion animal; breed characteristics; disease status; and feed selection. Intensive breeding (7–8 litters of 7–9 young/year) requires healthy stock, high-energy diets, and no evidence of enterotoxemia. Five and six breeding cycles per year can be produced on a maintenance diet such as 14% protein and 20% fiber. Seven and eight cycles per year require a different composition, that is, 17% protein and 17% fiber. Implicit in higher protein rations are higher grain and higher starch (high energy), which predispose to enterotoxemia if the rabbit carries potentially enteropathogenic bacteria or is not managed properly.

Postpartum estrus occurs in most does 2–11 days after kindling, and mating may occur at this time. Post kindling days 14–28 are heavy lactation days, and conception is often unsuccessful during this period. In the five cycles/year schedule, each breeding cycle is 73 days. Thirty to 40 young

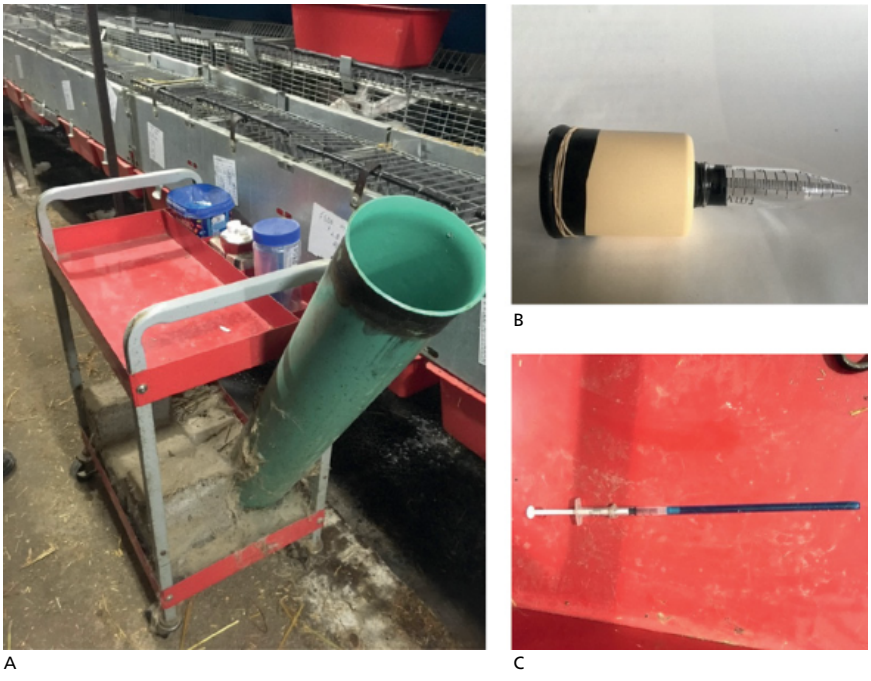


FIGURE 2.26. Equipment for artificial insemination of commercial meat rabbits. A. Breeding cart and doe restraint device. Doe is positioned head down in tube with hind end and genital papilla facing upward. B. Artificial vagina with attached collection tube. C. Insemination pipette. Courtesy of M. & J. Sanders.

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are produced annually. In the eight cycles/year schedule, each breeding cycle is 45 days with 40–50 young produced yearly. Approximately 40 fryers (i.e., fattening rabbits) per doe per year are needed to break even financially, but many commercial operations aim to produce 56 fryers per doe per year to increase profitability. Success of postpartum conception depends upon the doe condition, nutrition and disease status, and size of the litter being suckled.

A younger age at first breeding, shorter intervals between insemination, and shorter intervals between parturition are all causes of poor body condition and reduced litter size and numbers of kits weaned for primiparous does. Waiting to rebreed at day 32 postpartum helps to ensure these young does have regained adequate body condition and significantly improves fertility and fecundity.

Group Housing Production

Postpartum mating often occurs in animals reared in harem groups. Successive litters sometimes live together, though risk of maternal neglect is high for the youngest litter. Rabbits of different ages and litters may share nests, but stronger young survive at the expense of the smaller members. Disease is typically more common among group-housed rabbits. Thus, there are several significant limitations to successfully using this breeding method compared to other production schemes previously described. For efficiency and to reduce disease the weaned young are generally removed from breeding females and raised separately as littermates or in larger groups in floor pens or parks.

Pregnancy Detection

Abdominal palpation 10–14 days after breeding will usually detect pregnancy. Ultrasound diagnosis and radiographic evaluation can also be used. Breeding failure detected at 10–14 days usually indicates a problem with individual rabbit fertility, whereas resorption detected at 28 days after initial pregnancy diagnosis is usually a husbandry problem.

A suggested method for palpation to detect pregnancy is to (1) hold the nape of the doe's neck with one hand; (2) place the other hand under the body between the hind legs and slightly in front of the pelvis; (3) place a thumb on one side and fingers on the other side of the horns of the uterus (embryos will be grape or marble-sized, and ventral in the abdominal cavity); and (4) gently rub the thumb and fingers against the doe's abdomen to distinguish the embryos from fecal pellets. Alternatively, the rabbit can be cradled in dorsal recumbency for palpation (Figure 2.27). Tense abdominal muscles will make detection of the uterus difficult.

Pregnancy

The rabbit's gestation period lasts 30–33 days, with an average of 32 days. Litters retained longer than 34 days are usually stillborn or contain large or abnormal fetuses. Pregnant rabbits are particularly sensitive to fetal loss at 13 days, when placentation changes from the yolk sac to the hemochorial type, and at 23 days, when fetuses are more readily dislodged. Within 1 week of becoming pregnant, estrogen levels increase with respect to progesterone, the hair follicles relax, and the doe constructs a hair and material nest in a suitable box. Nest construction improves with successive litters. Because litter survival significantly improves with appropriately prepared nests, provision of nesting materials is recommended, particularly in summer when less hair is shed, and winter when more insulation is required. Straw, wood chips, sawdust, shredded paper, or leaves have been used to supplement nest building. Strong-smelling beddings, such as aromatic softwood chips, should be avoided because of the potential for respiratory irritation. Nests that become wet should be replaced.



FIGURE 2.27. Palpating the female rabbit for pregnancy. Rabbits are palpated for pregnancy between 10 and 14 days of gestation and again at 26–28 days to detect possible resorption.

The nest box itself is a substitute for the underground burrow found in the wild and provides protection of both doe and young from predators. Boxes should be protected from damp weather, should not allow kits to escape because does will not retrieve their young, and should be sanitized easily. Boxes may have a solid floor, but the surface should not be completely smooth, as a higher incidence of splay-leg has been noted to occur when inadequate traction can be achieved by the developing neonate (Figure 2.28). Boxes may sit on the hutch floor, be attached to the front of the cage, or be subterranean and attached to the cage's floor. The subterranean box mimics the natural burrow, stops escape, and aids retrieval but may not be possible to install in multilayer caging systems. Boxes 41 cm (16 in) (length) × 30 cm (12 in) (width) × 30 cm (12 in) (height) or larger are preferred. The box should be present for at least 10 days and is usually removed at 2–3 weeks postpartum. A doe may not use the nest box and may scatter newborn young on the wire if the bedding in the box is damp, contaminated with urine and feces, or has an odor of disinfectants or predators. This typically results in rejection and death of the litter.

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FIGURE 2.28. Young rabbit with splayleg. Courtesy of E.D. Olfert.

Parturition (Kindling)

Young are usually born at night. Oxytocin (0.2–3.0 units/kg IM) may be used in cases of dystocia or disruptions in labor. During delivery, the doe should not be disturbed. Optimal litter size is 8–10, and stronger, larger members of overly large litters should be fostered onto lactating does with young approximately the same age and size. Scent transfer is not a concern when fostering by or before 3 days following parturition and cannibalism is rare in rabbits. When it occurs, it may be associated with dead or deformed young, a hyperexcitable, primiparous doe, placentophagy, environmental disturbances, or a low-energy diet.

Metritis and retained fetuses or placentas may alter maternal behavior and cause the doe to scatter and neglect young. Does that have experienced a difficult kindling should be palpated for retained kits and should not be re-bred. Maternal neglect has been associated with inadequate nest boxes, chilling or escape of offspring from the nest, disturbance of the doe (particularly when primiparous), and agalactia or mastitis.

Neonatal Period

Domestic rabbits at birth are virtually hairless with sealed eyelids and ear canals, have little crawling ability, and weigh between 40 g and 80 g, depending on breed and litter size. Because of this, neonates are unable to maintain a stable body temperature if unfed or if the ambient temperature changes dramatically. Adequacy of ambient temperature can be assessed by observing the position of the kits. In warm environments (37 °C or 98 °F), the young disperse and assume an extended posture. At 25 °C (77 °F) neonates group, curl up, and move toward areas of higher temperature. Although neonatal rabbits increase heat production during cold stress through brown fat catabolism, shivering, and huddling with nest mates, body temperatures may decrease rapidly if the ambient temperature decreases to less than the critical temperature of 35 °C (95 °F) on day 1, 32 °C on day 5, or 29 °C on day 9. Nest box floors heated to 27 °C (81 °F) minimize chilling and reduce perinatal mortality.

The principal organ of thermogenesis in neonatal rabbits is brown fat, primarily located in the interscapular area. This triglyceride-rich tissue is found in the young of many species.

Nursing

The doe produces colostrum for 2–3 days postpartum, and then milk quantity increases and composition changes (protein 10%, fat 12%, sugar 2%) to a maximum production of 200–250 mL/day by 3 weeks. Quantity then decreases dramatically at 4 weeks, when most young are weaned. High heat may suppress lactation in does, generally by suppressing feed consumption. Young rabbits require only seconds to attach to a nipple after the doe's arrival in the nest. Location of the nipples by neonates is dependent on odor cues from the milk in the nipple areas. This dependence on odor (and certain tactile) cues for nursing may explain why newborn rabbits are difficult to bottle feed and hand raise. The environmental temperature and the suckling activity are linked to the onset of urinary and alimentary activity in the neonate. Rabbits require little maternal care to develop normally. Nursing periods, except for the first day, are generally less than 3 minutes in duration. Several investigators have reported no significant differences between young rabbits with continuous access to the doe and young allowed access for only a few minutes in the morning or evening. The doe's time in the nest box is not related to milk production or to kit satiation. These observations are consistent with wild lagomorph behavior, in which the dam only visits the young once or twice daily. In the wild, this brief suckling period may decrease the risk of exposure of the young to predators. Does with sucking kits should be provided with a platform or step of sufficient size and height to allow the doe to rest away from the kits. This will also help to reduce kit injury by the doe.

The young begin eating maternal feces at 8 days, and wetting kits with milk stimulates urination. A primiparous mother has less milk than in subsequent litters, and litters of more than 10 may be too large for the number of nipples. In both cases, litter sizes may be reduced by fostering the strongest kits onto another doe. Orphaned or abandoned young may be fed a milk substitute with an eye dropper, doll's nursing bottle, or syringe without needle. Puppy or kitten milk replacer formula mixed as one part Esbilac® powder + two parts water has been used but will be deficient in protein and fatty acids compared to milk from the doe. At 2 weeks, young will begin eating fresh greens, and they will drink water from a bowl at 15–18 days. Overfeeding should be avoided.

Rejection is rarely a problem in domestic rabbits; young kits can be fostered readily with no special handling precautions.

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If a buck is present when a strange litter is introduced into a foster doe's cage, that buck may mark or chin the young and thereby protect them from doe aggression. In an established doe and litter group, the doe's odor guides and groups the young. Scent glands produce a secretion containing hydrocarbons, proteins, carbohydrates, esters and waxes, fatty acids (acetic and isovaleric), triglycerides, and steroids. The submandibular (or submental) and anal secretions, along with piles of feces and urine spray, are used to mark territories and individuals, whereas the inguinal scent is used to mark young rabbits and sexual partners. Chin-marking of does by bucks is a common behavior, especially after coitus and in new surroundings.

Weaning

Weaning naturally occurs 4–5 weeks postpartum. Weaning is stressful, and the young may decrease food consumption for 3 days, which may be related to a learning curve for operation of feeders and waterers. A dripping water valve attracts young kits, and observation of other rabbits assists with learning. Growth is affected minimally if weanlings are moved to a clean new cage, or if the doe is removed and the litter left in the familiar environment of the nest box and maternal cage. This procedure may reduce the stress that accompanies weaning.

Several experiments have been conducted to determine the effects of handling young rabbits on subsequent behaviors, specifically exploratory, approach, sleep, and sexual behaviors. In these studies, the young were usually of the Dutch belted breed and were handled in various ways between days 1 and 20. Handling was restricted to 3 minutes daily, during which time the young were removed from the nest box, placed into a container with bedding, and then returned into the maternal nest. Although the experimental protocol varied, handled rabbits became more active, were more often awake and more exploratory, approached novel stimuli more often, and reached sexual maturity at an earlier age. This was more closely associated with stimulation occurring between days 11 and 20 than days 1 and 10.

Disease Prevention

The general recommendations for husbandry and disease prevention listed in Chapter 1 should be observed, especially the removal of ammonia from the rabbit's environment through appropriate waste management and hygiene practices. Common management practices with rabbits include periodic trimming of toenails and the exclusion of dogs, cats, and other animals, including insects, from the rabbitry. Mesh flooring, if used, must be selected to minimize injury to limbs. Vaccination is not routinely practiced in rabbits, although vaccines for the poxvirus disease, myxomatosis, have been used during outbreaks outside of North America. In recent years, rabbit hemorrhagic disease virus (RHDV) has become more prevalent in North America, and both companion and meat rabbits may require vaccination (see Chapter 5).

Special consideration should be given to neonatal and weanling rabbits in terms of minimizing disease. The nest box should be sanitized before use and kept clean and dry during use. Special provisions may be necessary to provide accessible food and water to young and to facilitate training to use feeders and waterers during the weaning period.

Table 2.2. Biodata: rabbits.

Adult body weight: male (buck)	2–5 kg
Adult body weight: female (doe)	2–6 kg
Birth weight	40–80 g
Body surface area (cm^2)	$9.5 \times (\text{weight in grams})^{2/3}$
Rectal temperature	38.5–40.0 °C (101.3–104 °F)
Diploid number	44
Life span	5–6 yr or more
Food consumption	5 g/100 g/d
Water consumption	5–12 mL/100 g/d
GI transit time	4–5 hr
Breeding onset: male	6–10 mo
Breeding onset: female	4–9 mo
Cycle length	induced ovulator
Gestation period	30–33 d
Postpartum estrus	48 hr
Litter size	4–10
Weaning age	4–6 wk
Breeding duration	1–3 yr
Commercial	7–25 litters
Young production	2–4/mo
Milk composition	12.2% fat, 10.4% protein, 1.8% lactose

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Public Health Concerns

Diseases of major public health importance in domestic rabbits are relatively rare. Salmonellosis, tularemia, rabies, ringworm (dermatophytosis), tuberculosis, and toxoplasmosis have been reported in domestic rabbits. Rabies vaccinations are not licensed for use in rabbits in North America and are not given except in cases of high exposure probability, such as after a local rabies outbreak in wildlife when rabbits are housed or spend time outdoors. Wounds caused by rabbit scratches may become infected with *Pasteurella multocida* or other bacteria, but this is rare.

Uses in Research

Rabbits are an important research animal. Approximately 394,100 rabbits were used in research in the United States from 2019 to 2021 (USDA Animal and Plant Health Inspection Service), and approximately 15,236 were used in the same period in Canada (Canadian Council on Animal Care). Rabbits are used most frequently as sources of hyperimmune sera and antibody. Other uses of rabbits in biomedical investigations include ocular research, dermal and reproductive toxicology, cardiovascular disease, oncology, infectious diseases, and medical device testing.

Biodata

The values listed in Table 2.2 are approximations and may not represent the normal range in a given rabbit population.

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Journal of Exotic Pet Medicine and *Veterinary Clinics of North America: Exotic Animal Practice* are excellent resources for companion animal practitioners. *World Rabbit Science* is an open access journal produced by the World Rabbit Science Association and is geared to meat rabbit production and veterinary care. The American Association of Laboratory Animal Science (AALAS) publishes several scientific journals on species commonly worked with in laboratory animal medicine, including rabbits. The Talk Origins Archive gives useful information about the evolution of various animal species, http://www.talkorigins.org.

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THE GUINEA PIG

The guinea pig or cavy is a docile medium-sized rodent popular as a companion, show, or research animal or, in parts of Latin America and elsewhere, as a food animal. Guinea pigs are notable for their fastidious eating habits, absolute dependence on dietary vitamin C, relatively long gestation period, large and precocious young, and rather messy living habits.

Origin and Description

The domestic guinea pig or cavy, *Cavia porcellus*, belongs to the Caviidae family in the Suborder Hystricognatha and is related to wild and semi-domesticated cavies (*Cavia aperea*) still found in the mountains and grasslands of Peru, Argentina, Brazil, and Uruguay. Guinea pigs are gregarious, herbivorous (except for placentophagy), nonburrowing, crepuscular animals. Other New World hystricognaths include agoutis, degus, and chinchillas. Association with humans began as early as 5,000 B.C., and cavies were highly regarded in ancient Andean culture. They were used not only for food and companionship, often being kept inside dwellings as a ready supply of protein, but also for ritual sacrifice and other ceremonies. In the sixteenth century they were taken as curiosities to Europe, where they were bred selectively by fanciers, resulting in several coat colors and hair lengths. Today, guinea pigs are rapidly gaining popularity as a micro-livestock species in Africa and Asia. A group of guinea pigs can easily be managed by a family and can produce enough meat for personal consumption, as well as for supplemental income.

There are several breeds and varieties of domestic guinea pig as determined by the length, direction, and texture of the haircoat. The most common companion and laboratory variety is the English, American, or short-haired guinea pig, which has a uniformly short-haired coat. The Duncan–Hartley and Hartley strains are outbred stocks representative of the English variety and are available from a number of laboratory animal suppliers. Inbred strains are no longer commercially available. Other recognized breeds include Abyssinian, with short, rough hair arranged in whorls or rosettes, Silky, which has medium-length, soft hair, and Peruvian long hair or "rag mop" variety (Figure 2.29). Guinea pigs may be mono-, bi-, or tricolored. The varieties interbreed, and a profusion of colors and hair coats is possible, but accurate predictions of coat color inheritance are not. The American Cavy Breeders Association (http://www.acbaonline.com) currently recognizes at least 13 different breeds as show stock, while the British Cavy Council lists over 40 different breeds. In addition, two hairless varieties, the Skinny and the Baldwin, which are born with hair but lose it at weaning, have also been developed (see Figure 2.29).

Anatomic and Physiologic Characteristics

Guinea pigs have compact stocky bodies, with a short neck, short legs, round hairless pinnae, and no tails. They have four digits on the front feet and three digits on the hind feet. A curved toenail is present on the distal phalanx of each digit, which often requires trimming. Hairless areas include the plantar aspect of the feet, the ears, the skin caudal to the ears, and the skin around the two inguinal nipples. In haired breeds, the rest of the body is covered with large guard hairs with a finer undercoat. Similar to rabbits and other rodents, guinea pigs are obligate nose breathers and cannot vomit. Mature males (boars) weigh between 900 and 1200 g, while females (sows) weigh between 700 and 900 g. Guinea pigs bred for meat can weigh up to 2.5 kg or more. Their lifespan ranges from 2 to 8 years, averaging 5 years.

The guinea pig dental formula is 2(I1/1 C0/0 P1/1 M3/3) = 20 with a diastema or gap between the incisors and premolar teeth. All rodents are monophydont, meaning that they only have a single set of teeth. Guinea pigs use their chisel-shaped incisors for gnawing and to cut grass and hay. The incisors are open rooted and grow continuously and enamel is present only on the labial side. The incisor enamel of guinea pigs is white, in contrast to the yellow of other rodents. Incisors and molars can grow up to 2.0 mm/wk and the lower incisors are longer than the upper ones (Figure 2.30). The cheek teeth (molars and premolars) of guinea pigs and other hystricomorph rodents such as chinchillas are open-rooted and continuously growing, similar to rabbits, and occasionally require trimming. This differs from rats, mice, hamsters and gerbils, in which cheek teeth grow is finite. In guinea pigs the mandibular cheek teeth are convex on the buccal aspect, while the maxillary cheek teeth are convex on the lingual side. Because of this, overgrown upper teeth will project laterally into the buccal mucosa and overgrown lower teeth will extend medially, causing tongue lacerations and entrapment (Figures 2.31 and 2.32). The upper lip is divided into two halves by a cleft called the

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A B C D

FIGURE 2.29. Typical appearance of several guinea pig breeds, A: English short hair, B: Abyssinian, C: Peruvian, and D: Skinny pig. Courtesy of E.D. Olfert.



FIGURE 2.30. Normal guinea pig incisors. Note the relative lengths of the maxillary and mandibular incisors and the fleshy cheeks.

philtrum. The oral cavity is relatively long and narrow with a small gape, large tongue, and fleshy buccal pads that invaginate through the diastema and meet behind the upper incisors, making examination difficult. The soft palate is continuous with the base of the tongue and has an opening, the palatal ostium, which connects the oropharynx to the rest of the pharynx (Figure 2.33). This restricted opening makes tracheal intubation and oral gavage challenging in the guinea pig.

Guinea pigs are monogastric hindgut fermenters, with a long colon and a very large cecum that occupies most of the central and left side of the abdominal cavity and can hold up to 65% of the total gut contents. The cecum contains microorganisms that digest cellulose and add B vitamins. The stomach is undivided and lined entirely with glandular endothelium, and the small intestine lies primarily on the right side of the abdomen. Gastric emptying takes

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FIGURE 2.31. Normal guinea pig cheek teeth anatomy, as viewed with an otoscope. Courtesy of M. Taylor.

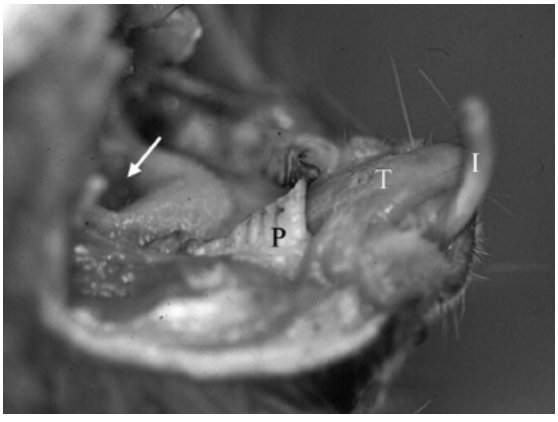


FIGURE 2.33. Palatal ostium (arrow) in a guinea pig taken at post mortem. In this animal, the premolars (P) are severely overgrown and have entrapped the tongue (T). The lower incisors (I) can be seen.

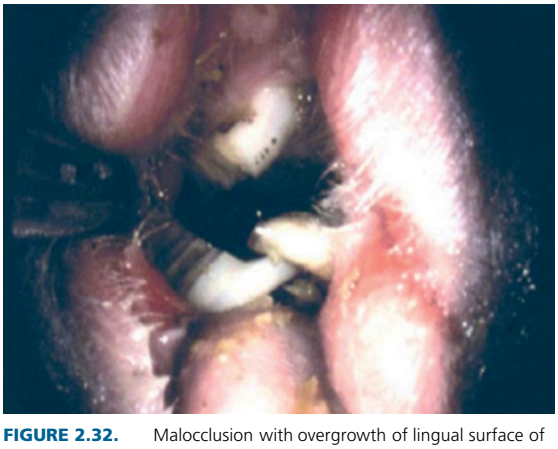


FIGURE 2.32. Malocclusion with overgrowth of lingual surface of molars, entrapping the tongue, as viewed with an otoscope. Courtesy of M. Taylor.

about 2 hours, and total gastrointestinal transit time is approximately 20 hours (range 8–30 hours). Like rabbits and other rodents, guinea pigs are coprophagic; however, the colonic separation mechanism in guinea pigs and other rodents is different from rabbits in that it uses a mucus trap instead of a retrograde motion mechanism. In rodents, a colonic furrow allows mucus and bacteria to be trapped and transported back to the cecum by antiperistalis, while less nutritious food matter continues to the distal colon for elimination. Unlike rabbits, the mucus trap simultaneously moves fluid and particulate material. Because of this, the feces and the nutrient-rich cecotrophs look very similar. In caviomorphs, such as guinea pigs and chinchillas, the nitrogen content in cecotrophs is 26–52% higher than in their cecal contents. Cecotrophs also contain high levels of vitamin B and protein. They are consumed directly from the anus with between 150 and 200 incidences per day, although obese and pregnant animals may eat feces from the cage floor. Guinea pigs are sensitive to certain antibiotics, particularly those that disrupt the microbial balance in the gastrointestinal tract. A decrease in intestinal Gram-positive organisms can favor overgrowth of *Clostridium difficile* and lead to enterotoxemia and death (see Chapter 3).

Guinea pigs have large tympanic bullae and the ear canal is relatively long and tortuous, making examination of the tympanic membrane difficult. They have a well-developed intracoronary collateral network, making it difficult to produce cardiac infarct by acute coronary artery occlusion. In immature animals, the functional thymus lies subcutaneously, on either side of the trachea, and within the neck tissues, although in some guinea pigs, a portion extends caudally into the precardial mediastinum. By about 12 months of age, the thymus involutes and is replaced by fatty tissue. The thymus may be located easily and removed, if necessary, to treat neoplasia.

Both male and female guinea pigs have two inguinal nipples, although sow nipples are longer and more prominent and mammary glands themselves are confined to the sow. Androgen-dependent sebaceous glands are associated with hair follicles and are most abundant along the dorsum and perianally. An accumulation of these glands just dorsal to the anus forms a noticeable waxy area and occasionally causes matting of the hair, which is more common in intact males and obese animals. The glands are used for scent-marking, and guinea pigs often walk or sit with them pressed against a surface. Both males and females have a well-developed perineal

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sac or diverticulum that separates the anus from the genital opening. This sac occasionally becomes filled with oily secretions, hair, and feces and must be manually expressed, especially in older intact males.

Guinea pig urine is opaque, often creamy to orange-colored, depending on food pigments and may normally contain some crystals. The adrenal glands are large and bilobed (Figure 2.34). The pubic symphysis remains cartilaginous in most animals and separates 7–8 mm (1/4 in) in pregnant animals prior to giving birth. The uterine artery provides the major blood supply to the ovary. The large seminal vesicles of the boar are bilateral, smooth, and transparent and extend approximately 10 cm into the abdominal cavity from their base in the accessory sex glands. To a casual observer, these elongated organs resemble a uterus (Figure 2.35).

Unlike rats and mice, guinea pigs exhibit lethal bronchiolar smooth muscle contraction after histamine administration.

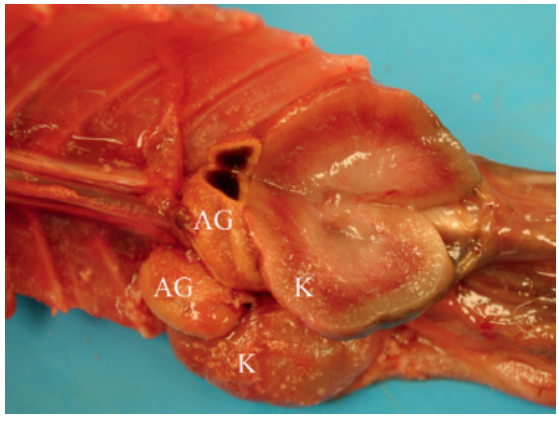


FIGURE 2.34. Adrenal gland (AG) and kidney (K) from a guinea pig. The normal guinea pig adrenal gland may be up to one-third the size of the kidneys.



FIGURE 2.35. Seminal vesicles from a mature boar. Courtesy of D.H. Percy.

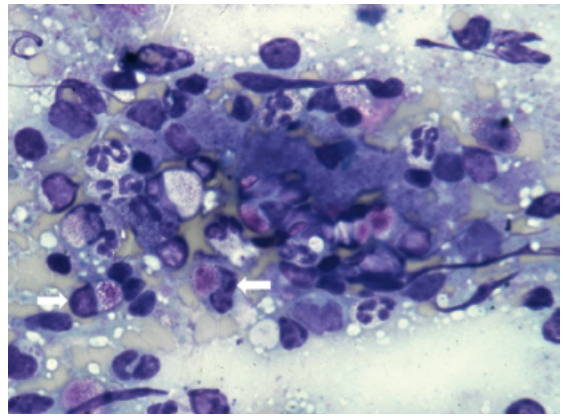


FIGURE 2.36. Kurloff cells (white arrows) in a peripheral blood smear from a mature sow. Courtesy of D.H. Percy.

Mature sows are an excellent source of serum complement, the protein complex involved naturally in immune and endotoxin reactions and used experimentally in serologic testing. Guinea pigs produce antibodies to specific proteins, and induction of anaphylaxis is an indicator of the presence of small amounts of antigen. Unlike the rabbit or chicken, the guinea pig injected with antibodies is protected from anaphylaxis.

Kurloff cells are large, mononuclear, granular lymphocytes, specifically natural killer (NK) effector cells with T-lymphocyte subset markers that are unique to guinea pigs and capybaras. They are found primarily in the thymus, spleen, liver, and lung, as well as various other tissues, and in the peripheral blood of pregnant animals. These cells contain large intracytoplasmic inclusions of glycoproteins and acid hydrolases (Figure 2.36). They proliferate during estrogenic stimulation and are found in highest numbers in the placenta, where they may function to protect fetal antigens from sensitized maternal lymphocytes and immune globulins. They may also be seen in peripheral blood smears on occasion. Another postulated function is surveillance against leukemic or other neoplastic cells.

Guinea Pigs as Companion Animals

Behavior

Guinea pigs are gentle, docile, and highly social animals that are relatively easy to maintain. They rarely bite or scratch but when excited will race around their pens, scattering feed and bedding. Guinea pigs seldom climb or jump out of pens with open tops, and a 25 cm (10 in) barrier will usually confine all but sexually mature males. They respond favorably to frequent, gentle handling and holding, and quickly become conditioned to squeal when they hear the refrigerator door open, in anticipation of a treat. They have a variety of vocalizations that correlate with at least 11 social behaviors, including social interactions (chut or purr call), aversion (chutter, hiss, whine), and injury or fear (whistle, squeal,

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scream). When happy, guinea pigs, and in particular, young animals, will hop quickly, sometimes turning slightly before landing ("popcorning"). When housed in groups, the dominant animal will often keep watch over the group, and other guinea pigs may hide behind this animal when startled. Guinea pigs are excellent swimmers. They sometimes may be seen sleeping with their eyes open.

Guinea pigs have certain behavioral characteristics that have important implications for both health and husbandry. As guinea pigs mature they develop rigid habits that must be accommodated if the animal is to thrive. Any changes in feed (taste, odor, texture, form), water, feeder, or watering device may cause the guinea pig to stop eating or drinking. This may result in fatal consequences, especially in pregnant females. Excited guinea pigs may stampede or "circle" and either trample the young or fall within the cage if there are multiple levels. A rectangular enclosure or barriers within the cage or enclosure reduce circling, but stampedes still occur.

Guinea pigs establish male-dominated hierarchies, and within these hierarchies subordinate animals may be chewed and barbered. Although these hierarchical colony arrangements are usually stable, strange males placed together, especially in crowded conditions or in the presence of a female in estrus, will fight. Neutering animals and providing increased, appropriately furnished space will increase success of social groupings as animals become sexually mature and will reduce unwanted pups.

Life Span

The breeding life of guinea pigs is from 6–8 months to 4 years, and they can live 8 years; however, they rarely survive in a home environment more than 5 years, and their litter size is reduced to 1–2 young/litter by 27–30 months of age.

Handling and Restraint

Guinea pigs are lifted by grasping under the trunk with one hand while supporting the rear quarters with the other hand (Figure 2.37). The two-hand support technique is particularly important with adult and pregnant animals. Injured lungs or liver may result from grabbing the animal around the thorax or abdomen without providing additional support. Holding the animal close to the handler's body will increase the animal's sense of security.

Housing

Guinea pigs may be housed in pens on the floor, in tiered bins, or in large "shoe box"-style cages (Figures 2.38–2.40). Guinea pigs are very social animals and should not be housed



FIGURE 2.37. Guinea pig being restrained in an upright position for a nail trim. Holding the guinea pig against the handler's body increases animal comfort.



FIGURE 2.38. Pen housing for a pair of pet guinea pigs. The open top and plastic-coated wire sides permit good air circulation within the cage. Free choice hay is available and there are two hiding spaces as well as manipulanda to investigate and chew. Courtesy of J. Ranger.

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FIGURE 2.39. Typical open-topped guinea pig tub with tubes and hiding places for paired animals.



FIGURE 2.40. Rack-type group housing for laboratory guinea pigs with plastic cage pulled out to demonstrate hut for hiding and manipulanda. Courtesy of J. Lofgren.

individually in a research or pet setting without strong justification. Young and breeder animals occasionally will climb out of bins even with cage sides of 25 cm (10 in high), and a mesh cage lid should be used to minimize accidents from falls and unplanned mixing of sexes. Solid-bottom cages are essential to prevent leg and foot injuries. Recommended space requirements for research animals are similar for the United States and Canada. Breeders should be provided with at least 1,100 cm^2 (180 in^2) of floor space per animal.

Beddings of wood shavings, shredded paper, or other material of plant origin may be used; however, cedar dust may cause respiratory problems, and small particles may adhere to the moist genitalia and impede breeding. A hiding area, such as a piece of large-diameter polyvinyl chloride (PVC) tube halved longitudinally, a small paper bag, a metal or plastic hut, or a commercially available house should be provided to allow a sense of security (Figure 2.41). The enclosure should be placed in a quiet place, out of direct sunlight, and where the ambient environment is stable.

Guinea pigs are housed at temperatures between 18 °C and 26 °C (65–79 °F), with an optimal ambient temperature at 21 °C (70 °F). Lower temperatures may decrease the survival rate of newborns. High ambient temperatures without adequate air flow predispose to sterility and heat stress; low temperatures and wet bedding predispose to respiratory disease. The relative environmental humidity should be between 40% and 70%. A 12 : 12 hour light : dark cycle is used commonly with 10–15 air changes per hour. Note that covered glass aquaria may not allow adequate ventilation for guinea pigs and can be difficult to lift and completely sanitize. Guinea pigs are messy pets, scattering bedding and food; and their urine is opaque, creamy yellow, and contains crystals. Cages, pens, and feeding receptacles should be cleaned and sanitized at least once weekly. Satisfactory cleaning procedures include washing the cages with a detergent and hot water or with a disinfectant solution followed by a thorough rinse. A weakly acidic solution may be needed to remove the urine scale.

Feeding and Watering

Guinea pigs are strict herbivores and are cecal fermenters, as are horses and rabbits. Unlike rabbits, however, guinea pigs possess endogenous lactobacilli and produce propionic acid as the primary fatty acid. Food intake is controlled not by calories ingested but by bulk consumed. Guinea pigs require specific amounts of calcium, phosphorus, magnesium, and

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FIGURE 2.41. Hiding places are important for guinea pigs and enhance feelings of security as well as providing spaces to rest away from others. Courtesy of J. Lofgren.

potassium, and regular feeding of table scraps, vitamin D–fortified cow's milk, or other animal feed is not recommended, as it may promote metastatic calcification, acidosis, ketosis, or skin disease from vitamin A or D toxicity. Deficiencies of vitamin A or tryptophan may lead to corneal lesions, and vitamin E deficiency leads to a muscular dystrophy. As described below, vitamin C deficiency is a major concern in guinea pigs, as they are unable to endogenously synthesize this nutrient.

Because guinea pigs are messy, feeders and waterers should be elevated above the cage floor to prevent contamination with feces and bedding. Guinea pigs learn readily to drink from suspended water bottles with sipper tubes or valves, but they are notorious for chewing on and playing with these devices. They often mix dry feed with water in their mouths and pass the slurry into the sipper tube, causing it to become blocked, or to drip and empty the bottle, leaving wet bedding and no access to water. Automatic watering valves that are located outside the cage or other devices that divert spilled or leaked water to the outside of the cage are preferred as they minimize wet cages and flooding. Automatic waterers must be checked frequently and lines and lixits must be cleaned and flushed periodically. Animals reared with water supplied in bowls or crocks may become dehydrated before finding water when it is provided by unfamiliar sipper tubes or as nipple valves of automatic watering systems. A water bottle should be maintained when switching to automatic waterers until it can be assured that all animals have made a successful transition.

Guinea pigs are fastidious eaters and may refuse to eat or drink if the feed or feeders are changed. They should receive a freshly milled, properly stored, pelleted, complete guinea pig diet, ideally, supplemented with hay. Such supplementation may improve production and growth and decrease obesity and dental disease, although pathogenic microorganisms may be introduced on hay or greens if they are contaminated. Adult guinea pigs will consume approximately 6 g of feed and 10–40 mL of water per 100 g body weight daily; these amounts vary with ambient temperature, breeding status, food and water wastage, and relative humidity. Guinea pig chows are provided as small pellets that contain approximately 18–20% crude protein and 10–16% fiber. Large amounts of feed wastage are associated with wire floor cages or use of feeders without inside lips. Small amounts of carrots, fresh fruits, and well washed fresh leafy greens may be given to guinea pigs as treats, but should not form more than 10% of the daily intake.

Guinea pigs, like humans and primates, lack the enzyme L-gulonolactone oxidase in the glucose-to-vitamin C synthesis pathway. Vitamin C is required for cross-linking lysine and proline in collagen fibers, which in turn are necessary for forming strong bones and blood vessels. Vitamin C is water soluble and is not stored in the body, making daily supplementation essential for good health. Guinea pigs have an absolute daily requirement of ascorbic acid of 10–25 mg/kg for maintenance and up to 30 mg/kg daily for pregnancy, although 2 mg/d may prevent signs of deficiency (i.e., scurvy). If ascorbic acid is not supplied in the feed, it can be added to the water (1 g/L), provided in tablet form (Oxbow, vitamin C tablets, https://oxbowanimalhealth.com/product/natural-science-vitamin-c-support) (Figure 2.42), or each guinea pig may be fed daily approximately one small handful or less of kale, parsley, beet greens, kiwi fruit, broccoli, orange, or cabbage. Even wood chips or shavings may contain small amounts of vitamin C. Carrots and lettuce are not good sources of vitamin C, and cabbage may contain goitrogens, so should be fed in limited quantities. The activity of vitamin C decreases as much as 50% in a

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FIGURE 2.42. Guinea pig taking an orange-flavored vitamin C tablet. Once accustomed to the taste, guinea pigs consider these tablets a treat.

24-hour period in water in an open crock and even faster if metal or organic material is present or if the room temperature is elevated. Feed containing ascorbic acid should be stored properly (cool and dry) and used within 90–180 days of milling, depending on the manufacturer's instructions. Newer stabilized forms of vitamin C, such as L-ascorbyl-2-phosphate, permit for longer feed expiration dates.

Guinea pigs should not be fed diets indicated for other species. Most pet store feeds for other rodents also have label indications for guinea pigs, which in most cases is misleading and inappropriate in that they have not been formulated taking into account the special nutritional requirements of guinea pigs. Rabbit food, for example, contains no ascorbic acid, and for guinea pigs, excessive levels of vitamin D. Also, guinea pigs have higher requirements for folic acid than do rabbits or other rodents.

Reproduction

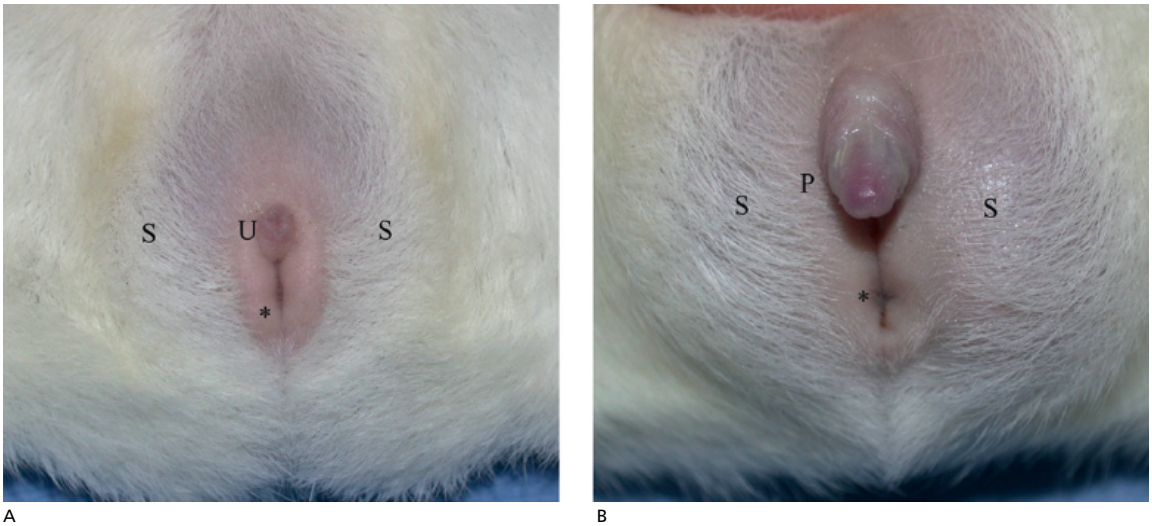
Sexing and Anatomy

Male guinea pigs (boars) are distinguished from females (sows) by their larger body size, smaller nipples, and a penis that can easily be extruded from the circular prepuce, revealing two prongs at its tip (Figure 2.43). The inguinal canals remain open throughout life, and the large 5–6 g testicles can either be withdrawn into the abdomen, or be present in scrotal swellings lateral to the anogenital line. The penis has a baculum (os penis), and accessory sex glands include long, smooth seminal vesicles (which may be mistaken by the inexperienced for a uterus), prostate, coagulating and bulbourethral glands, and vestiges of preputial glands. Mounting begins around 1 month of age, and ejaculations occur by around 2 months. Boars can reach puberty at 8 weeks, but 9–10 weeks is a more realistic average.

The sow has a Y-shaped anogenital opening, with the branches of the Y representing the urogenital opening, which is usually sealed with a vaginal closure membrane (Figure 2.45). The uterus is bicornate, with a single cervix.

Estrous Cycle

Sows reach puberty as early as 5–6 weeks of age. The estrous cycle lasts 15–17 days. During estrus the sow exhibits lordosis and mounts other sows. The estrous period itself lasts approximately 24–48 hours during which the

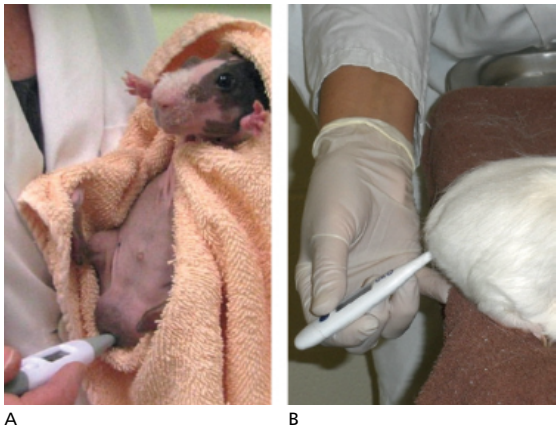


A B

FIGURE 2.43. A: Male genitalia of guinea pig with penis in prepuce (U, urethral opening; S, scrotal sac; *, anus). B: External genitalia of male guinea pig with penis extruded by digital pressure (P, penis; S, scrotal sac; *, anus).

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intact vaginal closure membrane perforates. The female accepts the male for 6–11 hours. If timed pregnancies are desired, mating can be detected by observation of the perforated vaginal membrane, presence of a vaginal plug, which remains in the vaginal opening for several hours, or sperm in a vaginal smear. Most sows have an estrus 2–15 hours postpartum, at which time 60–80% will become pregnant if mated.



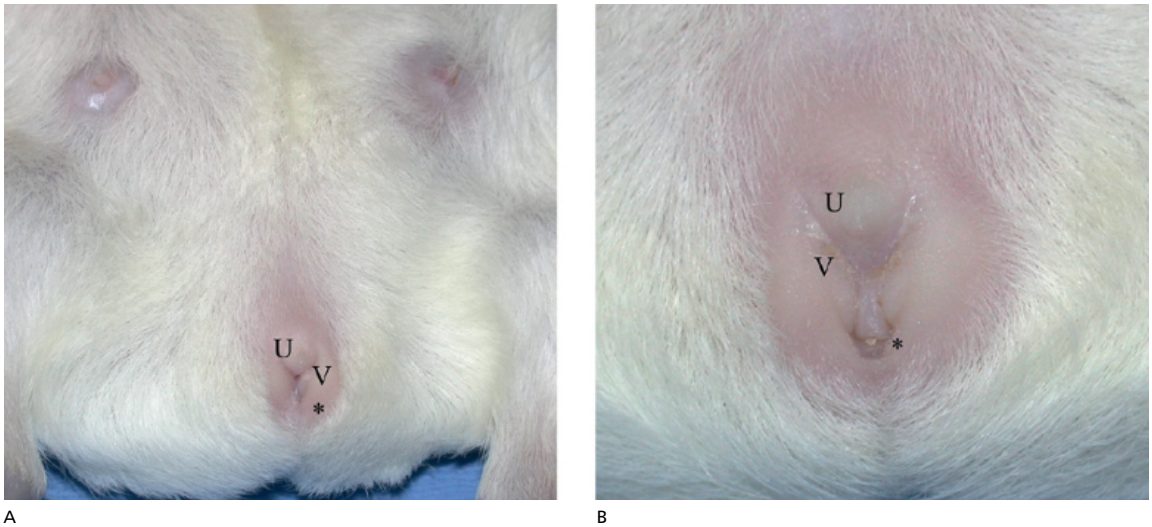
A B

FIGURE 2.44. The anus of the guinea pig is difficult to see in a conscious animal. A rectal temperature may be obtained by holding the animal upright (A*) or for a larger animal, positioning the hind end of the animal at the edge of the exam table and inserting the thermometer at an angle (B). *Courtesy of Calgary Avian and Exotic Pet Clinic.

Breeding Programs

Females should weigh approximately 400 g (2–3 months of age) and males 650 g (3–4 months of age) before breeding. For harem breeding, one boar is housed in an adequate-sized solid-bottom pen (1,100 cm^2 per animal) with 1–10 sows. Size requirements of the pen will limit the number of females housed with a boar. In intensive harem-style breeding systems, which use the postpartum estrus, the sows and boar remain together for their entire breeding life (approximately 18 months), and the young are removed at weaning. In this "continuous" system, a sow may produce up to 5 litters (12 young)/year. In a non-intensive system, the sows are removed for delivery and are rebred after weaning (3.5 litters or 9 young/year). In the discontinuous system, remating occurs only after weaning. Another variation is to return the sow alone to the harem for 6–12 hours to permit postpartum breeding. The sow is then returned to her young. Litter intervals in guinea pig colonies range from 80 to 96 days, and 0.7–1.4 young are born per sow per month. In commercial colonies, breeders are retained for approximately 18 months, and companion guinea pigs may reproduce for up to 3 years.

A receptive sow prowls and runs about the cage, mounts other sows, and assumes lordosis, which can also be elicited if the rump is stroked. After one or two intromissions, mating ceases and the copulatory plug remains in the vaginal opening for several hours. Two-thirds or more of matings are fertile, and implantation occurs in 1 week. Progesterone from the corpora lutea continues for 3 weeks, then placental hormones maintain pregnancy. Artificial insemination is not a practical



A B

FIGURE 2.45. A: Female genitalia of a mature sow during estrus phase (V, vaginal opening; U, urethral opening; *, anus). The urethra opens directly to the outside via a small papilla cranial to the vaginal orifice rather than into the vestibule of the vagina, as in many other mammals. The two inguinal nipples are readily apparent. B: External genitalia of female guinea pig (V, vaginal opening; U, urethral opening; *, anus). In this animal, the genital opening is sealed with a vaginal closure membrane.

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technique for guinea pig breeding. The placenta is hemomonochorionic, and trophoblasts are in direct contact with maternal blood. During the 59- to 72-day pregnancy (average 68), the normal 2 g uterus increases to 300 g, and up to one-third of the total maternal weight is due to fetuses (Figure 2.46). Fetal masses are palpable from 15 days to term. Animals are not fed prior to palpation, and the handler places a thumb on the iliac crest and the first two fingers on the ventral midline. The abdominal cavity is then palpated on one side and then the other as the hand moves anteriorly. Fetal skeletons can be radiographed from 6 weeks of age (Figure 2.47).

The fibrocartilaginous pubic symphysis, under the influence of the hormone relaxin, begins to separate during the latter half of gestation and continues parting until, at 48 hours prepartum, a palpable gap of around 15 mm is present. At parturition, this opening may reach 2.5 cm or more (approximately 1–1.5 in). If the first breeding is delayed past 8–10 months, the symphysis separates less easily, and fat pads occlude the pelvic canal.



FIGURE 2.46. Pregnant sow shortly before parturition. The sow's abdomen is markedly distended with pups. Courtesy of D. Smith.

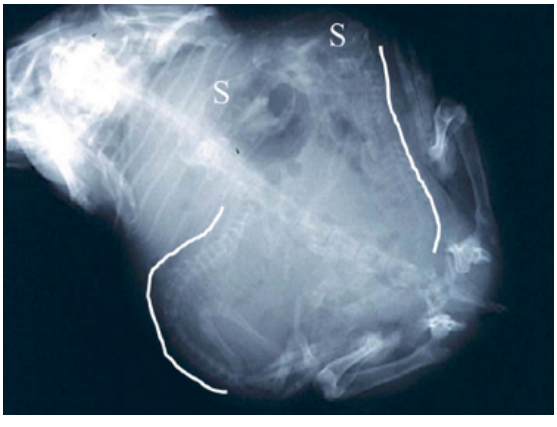


FIGURE 2.47. Radiograph of a pregnant sow with two pups. The skulls (S) and vertebral columns of the pups are clearly visible (white lines).



FIGURE 2.48. Five neonatal guinea pig pups within hours of birth. Pups are precocious at birth and are fully furred with open ears and eyes.

Such impediments may lead to dystocia, especially when small litters of large young are involved. Cesarean section, digital manipulation, or oxytocin carefully delivered at 1–3 units/kg may be needed to ensure delivery or death may result.

A normal delivery occurs over a half-hour period, with several minutes between births. First litters are smaller in number than subsequent ones. Guinea pig young are born fully furred with eyes open and teeth erupted, and within a few hours they are walking unsteadily and eating and drinking from pans (Figure 2.48). Food preferences are established and imprinted within a few days of birth. Pregnant sows may be separated or remain together, although in harems one sow's milk may be stripped by the larger young of other sows. Sows do not build nests.

Following birth, the young are cleaned and the placenta is eaten. Any dead or live premature fetuses should be removed from the enclosure promptly. The pubic symphysis closes within 24 hours. Two or three young weighing 70–100 g each are born (range: 1–6), and young weighing 60 g or less seldom survive. The young may be trampled if the adults are crowded or become excited. If the sow abandons the young before they are a week old, or if the young are weaned very early, mortality may be high. Problems with ear chewing and trampling are reduced if the young and sow are removed to a nursery before or soon after birth.

Endocrine control of gestation in the guinea pig is similar to that in the horse, monkey, and human in that the gestation period may be divided into trimesters of approximately 3 weeks. In many instances, pregnancy is maintained after ovariectomy at 25 or more days. The guinea pig has been used

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to study the effects of hormones and endocrine glands on pregnancy. Despite having only two nipples, guinea pigs can raise litters of 3, 4, and more young likely because of the pup's ability to eat solid food shortly after birth.

Neonatal Life

Neonates are precocious and nearly self-sufficient at birth. Although the young can eat or lap food from small bowls, syringe or bottle feeding (using the tiniest nipples available) for several days may be needed if they are neglected or rejected by the dam. The pup receives all its maternal antibody from the placenta, so there is little concern about requiring colostrum at birth. Hand rearing requires regular stimulation of defecation and urination and the provision of a heat source and a soft, fleece-lined nest box for approximately a week. Guinea-pig-specific infant formula may be available at specialty exotic veterinary clinics. It is important not to force feed as guinea pig infants may aspirate. Equipment should be washed and rinsed thoroughly after use, and hands should always be washed before and after handling infant guinea pigs. A small scale can be used for daily weighing to ensure that pups are growing. Additionally, in breeding operations, experienced females allow young other than their own to nurse; thus, foster nursing can be used to establish SPF colonies.

Under normal circumstances young guinea pigs can attach to nipples on day 1, and during the first week more time is spent nursing in the daytime. The dam remains immobile during the first few minutes of nursing, and auditory signals and other cues may elicit licking by the sow. The sow will nurse the pups for up to 3–4 weeks, but they may be weaned as early as 2 weeks of age without detriment. Neonates imprint on specific feeds very early in their lives, and their impression of what is food and what is not food persists stubbornly into adulthood.

Guinea pig milk contains approximately 4% fat, 8% protein, and 3% lactose. Milk production peaks to 65 mL/kg BW/day between days 5 and 8, then ceases at approximately 18–30 days, and the young are weaned at 14–28 days or between 150 and 200 g. Males make better breeders as adults if they remain socially housed to at least 30 days of age with their siblings and dam.

Disease Prevention

The general husbandry and disease prevention admonitions listed in Chapter 1 should be followed for guinea pigs. Guinea pigs scatter their bedding into feeders and crocks, are susceptible to *Bordetella bronchiseptica* pneumonia, have an absolute requirement for dietary ascorbic acid, and are fastidious eaters. If the food is changed, guinea pigs may refuse to eat. Because of *Bordetella* spp. susceptibility, guinea pigs should not be co-housed with rabbits, cats, dogs, and other species that carry this organism.

Public Health Concerns

Diseases of public health significance in guinea pigs are rare. Guinea pigs may carry bacteria (*Bordetella* spp., *Salmonella* spp., *Yersinia pseudotuberculosis*, *Streptococcus* spp.) that are potential human pathogens, but transfer of these infections to

Table 2.3. Biodata: guinea pigs.

Adult body weight: male	900–1200 g
Adult body weight: female	700–900 g
Birth weight	70–100 g
Body surface area (cm^2)	
700–830 g	$9.2 \times (\text{weight in grams})^{2/3}$
200–680 g	$10.1 \times (\text{weight in grams})^{2/3}$
Body temperature	37.2–39.5 °C (99–103.1 °F)
Diploid number	64
Life span	5–7 yr
Food consumption	6 g/100 g/d
Water consumption	10–40 mL/100 g/d
GI transit time	8–30 hr
Breeding onset: male	600–700 g (3–4 mo)
Breeding onset: female	350–450 g (2–3 mo)
Cycle length	15–17 d
Gestation period	59–72 d
Postpartum estrus	Fertile, 60–80% pregnancy
Litter size	1–6
Weaning age (lactation duration)	150–200 g 14–21 d
Breeding duration	18 mo (4–5 litters) to 4 yr
Young production (index/female)	0.7–1.4/mo
Milk composition	3.9% fat, 8.1% protein, 3.0% lactose

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humans would be most unusual. Allergies to guinea pig dander and proteins are common, and commercial shampoo preparations intended to remove antigens from animal fur may reduce human allergic exposures. The guinea pig sarcoptic mite, *Trixacarus caviae*, can cause transient dermatitis in people, but this is uncommon and usually self-limiting.

Uses in Research

Approximately 180,000 guinea pigs are used annually in research in the United States and approximately 15,000 are used annually in Canada. Guinea pigs are used in studies that involve anaphylaxis, skin sensitization, delayed hypersensitivity, genetics, ketoacidosis, scurvy, leukemia, allergic encephalomyelitis, ulcerative colitis, immunology, auditory function, and infectious diseases including tuberculosis. Complement commonly obtained from guinea pig serum is used in complement fixation tests to diagnose infectious diseases. Various biochemical and pharmacologic tests are also conducted commonly in guinea pigs.

Biodata

The values listed in Table 2.3 are approximations only and may not represent the normal range in a given guinea pig population. Sources consulted are included among the comprehensive texts listed in Chapter 1 and in the publications listed in the reference section below.

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Online Resources for Guinea Pigs

https://oxbowanimalhealth.com/blog/how-to-care-for-your-guinea-pig—Oxbow.
www.acbaonline.com—American Cavy Breeders Association.
https://www.thesprucepets.com/guinea-pigs-as-pets-1236837



THE CHINCHILLA

Chinchillas are noted for their soft, luxurious fur, long gestation period, precocious young, and long life span. They are raised in captivity for the fur trade, as companion animals, and for research. Their relatively large tympanic bullae make them a useful animal model for auditory research. Chinchillas require a daily dust bath to maintain the integrity of their coat, which has approximately 60 hairs per follicle.

Origin and Description

Chinchillas are classified as caviomorph (New World hystricognath) rodents and are related to guinea pigs and degus. There are two recognized species of chinchilla: *Chinchilla chinchilla* (short-tailed chinchilla) and *Chinchilla lanigera* (long-tailed chinchilla). *C. chinchilla* is the species most commonly kept as a companion animal and worked with in research. These gentle, relatively quiet, gregarious, and nocturnal rodents are native to the dry, cool Andes Mountains of South America, and live in large colonies inhabiting burrows or rocky crevices at elevations of 3,000–5,000 m. Their natural diet is high in fiber and low in energy, consisting of grasses, cactus fruit, leaves, bark, and the occasional insect. *C. chinchilla* has recently been downgraded from critically endangered to endangered by the International Union for Conservation of Nature since fur farming of this species has helped reduce illegal hunting and trapping in the wild. However, *C. lanigera* has been upgraded from vulnerable to endangered due to a 36% decline in population over 15 years and a very small area of occupancy in the wild.

Anatomic and Physiologic Characteristics

Domesticated *C. lanigera* are larger than their wild counterparts, with skulls 16% longer and 6% wider, on average. Female chinchillas are generally larger than males and have a prominent urethral papilla, which can be confused with a penis by inexperienced observers. In addition, the testicles of the male are retractable and are not always obvious on physical exam. The anogenital distance is the most dependable way to determine sex and can be reliably used at any age. In mature males, this distance is approximately 1 cm (2/5 in), which is about twice that of the female. Adult male chinchillas are called bucks and weigh between 400 and 500 g. The larger females are referred to as does and weigh between 400 and 600 g. Their life span is remarkably long for a rodent, reaching up to 18 years or longer.

Selective breeding has resulted in a variety of coat colors, including shades of black, white, beige, and blue, in addition to the wild-type gray. Some coat colors, such as white, are lethal in the homozygous state. *C. lanigera* has a large head, short forelimbs, long muscular hindlimbs and a large bushy tail, which is held off the ground and curled toward the body. When they are fluffed up they appear quite large, but their appendicular skeleton is relatively fragile. They have four digits on each foot each with a rounded soft nail that rarely requires trimming. The palmar and plantar surfaces of the feet are hairless. Chinchillas often sit upright, supported by their long hind legs, and use their forepaws for holding food or manipulating food or other resources.

The eyes of chinchillas have large corneas and a dark iris with a vertical pupillary slit. The retina lacks visible blood vessels. Like many other rodents, the upper lip is divided by a philtrum. They use their long whiskers to navigate in the dark. Their large, round ears are thin-walled and are used for thermoregulation, and the tympanic bullae are remarkably large. Not surprisingly, chinchillas are sensitive to noise and startle easily. They are nasal breathers and are unable to vomit.

The dental formula of a chinchilla is 2(I1/1 C0/0 P1/1 M3/3) = 20 and all teeth are open rooted (aradicular) and grow continuously, the incisors growing 4–6 cm/year (Figure 2.49). The enamel on the labial side of the incisors is pigmented yellow-orange. Incisors that are pale yellow to white may be indicative of a systemic calcium deficiency. The incisors are worn to a chisel-shaped cutting edge due to the rostral-caudal movement of the jaw during feeding. Similar to guinea pigs, chinchillas have upper lip skin folds that invaginate through the diastema to meet behind the upper incisors

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FIGURE 2.49. Normal chinchilla incisors. Note the relative lengths of the maxillary and mandibular incisors and the fleshy cheeks. Courtesy of Glen and Rebecca Grambo.

resulting in occlusion of the incisors outside the mouth. The clinical crown of the cheek teeth (i.e., the portion of the premolars and molars above the gingiva) is very short, and the occlusal surface of the cheek teeth is more horizontal compared to guinea pigs.

The oral cavity is narrow and the soft palate is continuous with the base of the tongue with a hole in it leading to the caudal passage, the palatal ostium. Like guinea pigs, chinchillas are monogastric herbivores and the stomach is large and simple. The intestines of the chinchilla are long with a large, coiled cecum on the right side of the abdomen that holds a smaller volume of intestinal contents than in guinea pigs and rabbits. The proximal colon is highly sacculated, and the terminal colon is smooth. The gut transit time is 12–15 hours. Like rabbits and other rodents, chinchillas are coprophagic with a colonic separation mechanism similar to guinea pigs and other rodents (see Chapter 2, guinea pigs).

The thymus is located entirely within the thorax. The left lung has three lobes, whereas the right has four. A right coronary artery is absent. Heart murmurs are a common finding on routine clinical examination and can be heard in up to 23% of patients. These murmurs may not be associated with other cardiac anomalies. The liver has four lobes: right, left, middle, and caudate, and chinchillas have a gall bladder. Chinchillas originate from an arid environment and rarely drink water in the wild. Their relatively large renal medulla allows them to conserve water by producing highly concentrated urine. Chinchillas have three pairs of mammary glands, one pair in the inguinal area and two in the lateral thoracic area.

Chinchillas have large tympanic bullae, which allow easy access to the middle ear, and they share similar anatomy and physiology of the inner ear, range of hearing, and age-related hearing loss (presbycusis) with humans, making them popular for auditory studies. The brain of chinchillas is supplied only by a vertebral–basilar artery system and internal carotid arteries are absent.

Chinchillas as Companion Animals

Behavior

Today, less than 50,000 chinchillas are kept as companion animals in the United States. Chinchillas are primarily nocturnal in the wild, but are often active during the day in captivity. They have a friendly, appealing, inquisitive nature and are not naturally aggressive toward humans. Chinchillas are odorless, quiet, and easy to maintain, provided they are fed and housed correctly. They enjoy being petted and cuddled if they are habituated to gentle handling. Because they use their mouths to explore their surroundings, they may lightly nip their handlers. Chinchillas may become stressed by loud noises and activity and should be kept in a quiet, cool area of the house. As social animals, they should be housed in same-sex pairs or groups, or if housed individually, given ample human interaction. Chinchillas are less vocal than guinea pigs and their normal communication is a soft, high-pitched grunting sound. They can also bark when angry or defensive and occasionally make a honking noise for attention. If they sense danger they will stand on their hind legs and make a warning whistle sound. Chinchillas can also scream in response to extreme fear. Chinchillas should be exercised outside their cage or enclosure, and they are good climbers and jumpers, often banking off walls and furniture. They will also use running wheels for exercise, and solid ones are preferred to minimize foot and leg injuries. They require safe items to chew as they are curious and may chew furnishings and cords when unsupervised. They also use their mouths to explore and will manipulate metal chains and other toys with their tongue and lips. Chinchillas can be territorial and may aggressively defend their home enclosure by standing and spraying urine in an upward stream toward the perceived intruder. Females may become aggressive when in estrus or post-partum, especially toward males. Intact males housed in groups may fight. Chinchillas are fastidious groomers, and require a dust bath, which should be accommodated in captivity. Like guinea pigs, they do not adjust very readily to changes in their environment. In the wild, chinchillas are crepuscular, like guinea pigs.

Life Span

The breeding life of a chinchilla lasts approximately 3 years, and their average life span is 10 years, although they can live to be 18 years of age or older and they are used as a research model for longevity.

Handling and Restraint

As for other rodents, frequent bouts of gentle handling provided when the animals are very young or when newly acquired will reduce fear and habituate them to being picked

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A



B

FIGURE 2.50. A. Towel restraint for chinchilla*. B. Two-handed restraint for chinchilla. *Courtesy of Calgary Avian and Exotic Pet Clinic.

up. Providing animals with occasional food treats or petting during these sessions while talking in a soft voice will further encourage learning of positive human–animal interactions.

Chinchillas can be removed from their cage by firmly grasping the base of the tail and lifting while supporting the body with the other hand. They should never be picked up by the tail alone. They can be picked up and restrained within a towel. Alternatively, very tame animals can be gently grasped around the thorax, while supporting the hind end with the other hand (Figure 2.50). Excessive chasing around the cage, improper restraint, or even bumping into the cage may cause a phenomenon known as fur slip, in which a clump of fur is released, leaving behind a patch of smooth, clean skin. Fur slip is a protective mechanism used to evade wild predators and is caused by simultaneous release of hair shafts from the follicles as a result of a "fight or flight" response. Hair regrowth following fur slip or clipping can take several months, and the hair will often grow back a slightly different color.

Housing

Chinchillas are typically housed in metal or plastic solid-bottom cages or enclosures. Some owners choose to keep them in large, multilevel habitats constructed of untreated wood, plastic, or metal with coated grid or mesh wall panels (see Figures 2.51–2.54). When wood is used for construction it should be inspected regularly to ensure that it remains structurally sound and free from chewing damage. Mesh flooring should be avoided to reduce the incidence of limb or foot injuries, especially in young. Recycled paper products or wood shavings may be used as bedding substrate; however, resinous softwood or treated wood products have been associated with nasal irritation and other toxicities and should be avoided. Chinchillas are very active and will climb and jump given the opportunity. Safe items should be provided for gnawing, such as wood blocks, hard rubber toys and chew bones, as well as items that can be orally manipulated, such as plastic or steel chains affixed to the cage. Commercially available shelters, lengths of PVC food grade pipes, or other types of hide-boxes should also be provided for privacy. Chinchillas will perch on flat-topped structures and will also sleep in a soft, suspended hammock. Exercise outside the cage environment is also desirable where possible (see Figures 2.51–2.54).

Chinchillas require a dry, draft-free environment, with a temperature range between 16 and 21 °C (61–70 °F). They are very prone to heat stress (Figure 2.55) and can die if temperatures exceed 32 °C, but they can withstand temperatures of 0 °C if allowed to become cold adapted. Cold temperatures stimulate production of a thick hair coat.

A unique housing requirement of chinchillas is regular access to a dust bath to prevent fur from becoming matted with oily secretions (Figure 2.56). Dust should be offered in a shallow pan at a depth of 4–6 cm for about 10 minutes each day. Commercial products composed of silver sand, Fuller's earth, diatomaceous earth, and volcanic ash are readily available, or dust can be made with nine parts silver sand to one part Fuller's earth. The bath should be removed daily for cleaning and to prevent overuse. Unlimited access to dust baths can result in dry skin and conjunctivitis. In addition, dust baths should not be shared between enclosures to prevent transmission of diseases such as dermatophytosis. Dust baths should be withheld from near-term females and mothers with

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FIGURE 2.51. Typical plastic-coated wire multilevel cage for pet chinchilla.



FIGURE 2.52. Igloo shelter resource for chinchilla.

litters, as the dust may contribute to mastitis and uterine infection or get in the mouth and eyes of the young.

Chinchillas tend to choose one corner of the cage for urination, but will defecate anywhere. The fecal pellets have very little odor, and are normally well formed, dry, and easy to clean up. A light cycle of 12 : 12 hours light : dark with 10–15 air changes per hour is appropriate. Relative humidity should be kept between 30% and 60%. Cages and feed and water containers should be cleaned and sanitized at least once weekly by washing with detergent and hot water, followed by a thorough rinse.



FIGURE 2.53. Running wheel for chinchilla.

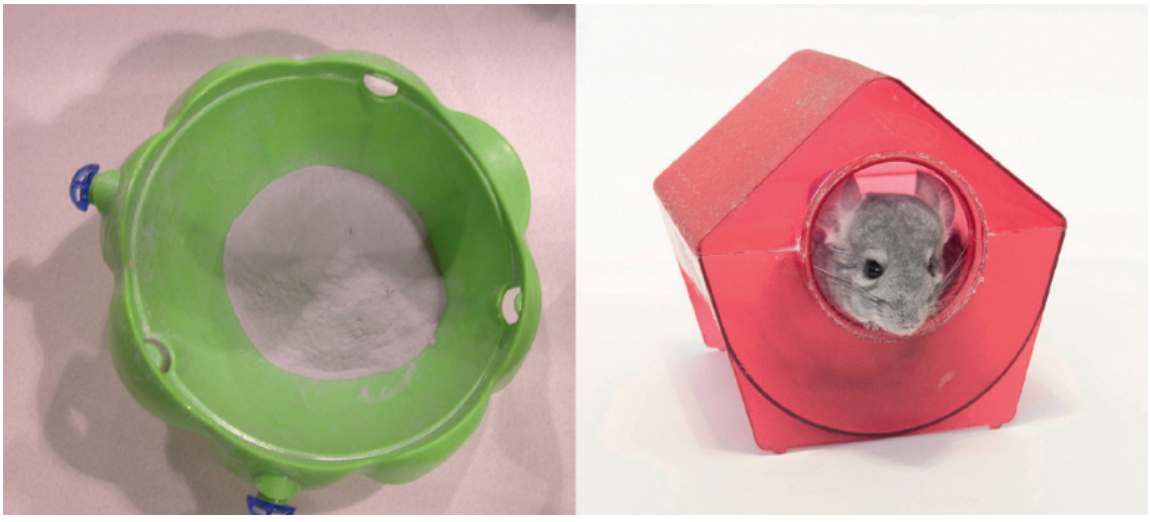


FIGURE 2.54. Cardboard box resource for chinchilla. Courtesy of Glen and Rebecca Grambo.



FIGURE 2.55. Overheated chinchilla with marked bilateral aural vascular dilatation. Courtesy of A. Gold.

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A B

FIGURE 2.56. Examples of chinchilla dust bath, open (A) and closed* (B). Dust for bathing is available commercially for chinchillas. *Courtesy of G. & R. Grambo.

Feeding and Watering

Chinchillas are monogastric, hindgut-fermenting herbivores. Their exact nutritional requirements have not been determined, but they thrive best with a high-fiber, low-energy diet with 16–20% protein, 25–55% fat, and 18% fiber. Chinchillas normally sit upright on their haunches to eat, holding their food with their forepaws. Commercial chinchilla pellets are larger than guinea pig pellets to facilitate holding. Commercial diets can be supplemented with free-choice grass hay. Grains and high-starch or sugary treats should be avoided to prevent upsetting their dietary balance. Small amounts of well-washed dark green leafy vegetables can be fed instead as treats. Suspended hoppers or heavy crocks prevent overturning and feed waste. Hay provided in elevated feeders permits individual pieces to be pulled through and helps to prevent boredom by making chinchillas work for access. Dietary changes should be made gradually to avoid gastrointestinal upset. Salt licks with trace minerals can also be offered. Nuts should be avoided due to their high fat content. An adult chinchilla should consume approximately 30 g (1 oz) of chinchilla pellets, 5 g (1 tsp) of raw, washed vegetables, and free-choice hay each day. Unlike guinea pigs, chinchillas do not require addition of ascorbic acid to their diet. Similar to most other rodents, chinchillas are coprophagic.

Wild chinchillas rarely drink water, as they are able to maintain their hydration by licking dew drops and eating plants. Despite this, captive chinchillas should always be provided with continuous access to fresh, clean water. Chinchillas prefer open dish drinkers; however, they will adapt to drinking from water bottles with either valves or sipper tubes, which are typically more sanitary and practical. Watering systems should be cleaned regularly to avoid contamination with biofilm-inducing bacteria, such as *Pseudomonas aeruginosa*.

Reproduction

Sexing and Anatomy

Anogenital distance is the most reliable method for sexing chinchillas, with the distance of 1 cm in the mature male being approximately twice that of the female. Females have a large urinary papilla, ventral to the vagina, which is often mistaken for a penis (Figure 2.57). The horizontal, slit-like vaginal opening is located between the urinary papilla and the anus. The vaginal opening is not always present due to a closure membrane that opens only during estrus and parturition. Females have a bicornate uterus two cervices. Both male and female chinchillas have two pairs of lateral and one pair of inguinal nipples but only the females have mammary glands associated with these. In general, the body size of females is larger than males. Males do not have a true scrotum, as the testicles can be withdrawn into the abdomen through the open inguinal canals. The penis is supported by an os penis (baculum) (Figure 2.58).

Estrous Cycle

Chinchillas are seasonally polyestrous in the northern hemisphere from November to May. The vaginal closure membrane opens during estrus, and the vaginal opening between the urethral papilla and anus appears reddened and slightly moist. Gentle pressure on the urinary papilla will usually open

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FIGURE 2.57. External genitalia of a mature female chinchilla (U, urethra; V, vaginal opening; *, anus). The urinary papilla of female chinchillas is larger than in female guinea pigs and may be mistaken for a penis.



FIGURE 2.58. External genitalia of a mature male chinchilla (P, penis; *, anus).

the vagina. If the chinchilla is not in estrus, the opening will not be present. The estrous cycle in chinchillas lasts 20–60 days, with an average of 35 days. The estrus period lasts 24–48 hours and is characterized by opening of the vaginal closure membrane, accompanied by vaginal reddening and discharge. A wax-like estrous plug 2.5–3 cm (1–1.2 in) diameter is normally ejected from the female at the onset of estrus, the function of which is unknown. Reddened nipples and restless behavior occasionally accompany estrus. Postpartum estrus occurs 2–48 hours after parturition, and a post lactation estrus occurs 35–84 days after parturition. Vaginal cytology can be used to determine stage of estrus with 70% accuracy. Generally females will have 2 litters/year.

Breeding Programs

Sexual maturity is reached at about 4–5 months of age in females and 7–9 months of age in males. Mating systems can be either monogamous or polygamous, although female chinchillas are monogamous in the wild. In captivity, a harem scheme is typically used, with one male for every four to six females. A polygamous breeding system is usually used for commercial operations. Each female resides in her own individual cage, which is connected to other cages by a tunnel. Females are restricted to their own cages by a flat metal disc attached to a collar they wear around their neck, which is slightly larger than the tunnel opening, preventing passage. Males are not fitted with collars and can move freely from cage to cage. This provides males with easy, unrestricted access to females, and an area where they can rest and escape.

If pair mating is used, new introductions should be attempted only after caging animals near each other for at least 1 week. Allowing intended mates to use the same dust bath may increase acceptance. Female chinchillas are the dominant sex, and the female should be placed into the male's cage so that she is in an unfamiliar territory. Interested males will make a cooing, chuckling noise, and both sexes may rub their chins on the floor. Receptive females will exhibit lordosis and lateral deviation of the tail and will allow the male to mount. Following mating, the female may become aggressive toward the male. Several escape and hiding places should be available, in which only one chinchilla can fit and turn around to face the attacker. Threats are expressed by growling, chattering teeth, and spraying urine. Severe trauma or death may occur if the male is unable to escape.

A quiet environment is needed for successful breeding. Mating usually occurs several times during the night. Loss of some fur from the female is normal during mating, but excessive fur slip may indicate the need to separate the pair. An ejaculatory plug is found in the vagina after mating. These plugs are approximately 3.75 cm (1.5 in) long and remain in place for several hours before falling out. Mating normally occurs at night and the best time to check for plugs is early morning.

Assisted breeding techniques, using electroejaculation and cryopreservation of spermatozoa, have also been extensively studied in the past 10 years by researchers at the University of Cordoba in Argentina to facilitate captive breeding programs for this endangered species.

The gestation period is 105–120 days, with an average of 110. Pregnancy can be detected by gentle abdominal palpation at 90 days gestation, although experienced personnel may be able to detect pregnancy as early as 60 days. At about 60 days the mammary tissue and teats begin to swell and the nipples become reddened. Pregnancy can also be detected by regular weighing; weight change is minimal during the first 6 weeks, but then increases rapidly. Improper handling of a pregnant chinchilla may result in abortion or absorption of fetuses. Poor housing and severe stress can also cause loss of a litter.

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The pregnant dam should be provided with high-quality chinchilla pellets and alfalfa hay. The gravid uterus occasionally puts pressure on the intestinal tract, causing constipation. Lush greens should be avoided due to the gaseous intestinal distension caused by fermentation.

Neonatal Life

The male can usually remain with the female during gestation and parturition and will participate in the care of the young. A group of chinchillas may communally raise their young. Chinchillas near parturition become inactive and anorectic and may become aggressive to a previously compatible mate. The perineal area, mouth, and nose become wet with amniotic fluid to signal the start of parturition, which generally occurs at night or in the early morning. The strenuous phase of labor usually lasts 1–2 hours or less. During that time, the female writhes and stretches, and may vocalize. The interval between pups ranges from a few minutes to several hours, and generally all pups are born within a 4-hour period. The female will continually lick her vent as each fetus emerges, and will use her teeth to pull the kits from the birth canal. The fetal membranes are normally eaten. A post-partum estrus occurs approximately 12 hours after parturition and lasts for 2 days after which the vaginal closure membrane reforms. If the female becomes intolerant of the male during this time, he should be removed until the pups are weaned.

Dystocia is uncommon; however, cesarean section should be considered if more than 4 hours of unproductive labor has elapsed. After labor the female should be palpated to ensure no fetuses remain, especially if she appears restless, as mummified fetuses are relatively common. Medical or surgical intervention may be required if mummified or stillborn fetuses are found.

Litter sizes average 2–3, although up to 6 have been reported. Dams don't normally build a nest, but nest boxes may decrease neonatal mortality caused by cold stress. Birth weight ranges from 30 to 60 g, and kits less than 25 g are unlikely to survive.

Newborn chinchillas are precocious and are fully furred with a complete set of teeth, and able to walk within an hour of birth. Their eyes open within 24 hours of birth and they are very vocal and normally make a continuous whimpering sound (Figure 2.59). Chinchillas sit on top of their young to nurse them and keep them warm. Weaning can occur as early as 6 weeks, although lactation can last up to 8 weeks. In the pet trade, chinchillas are separated from their mothers at 7–8 weeks of age and are usually sold at 3–6 months of age.

Orphaned kits can be fostered onto other chinchillas or even onto guinea pigs. If fostering is not possible, kits should be hand fed for 2–3 weeks until they are able to feed themselves. Feeding should occur every 2–3 hours using an eye dropper, and decrease as the kits mature and begin to take in food on their own. Newborn kits will begin to eat small amounts of solid food within the first week of life.



FIGURE 2.59. Two week-old chinchilla pups. Pups are born precocious.

Disease Prevention

Chinchillas must be kept in a dry, cool environment to prevent respiratory problems, and should be provided with a daily dust bath for maintenance of a healthy coat.

Public Health Concerns

Diseases of public health significance include infections with *Yersinia enterocolitica*, *Salmonella enterica*, *Serovar typhimurium*, *Streptococcus equi subspecies zooepidemicus*, *Listeria monocytogenes*, *Hymenolepis nana*, *Giardia spp.*, *Echinococcus multilocularis*, dermatophytosis, lymphocytic choriomeningitis virus (LCMV), tuberculosis, pasteurellosis, toxoplasmosis, and cryptosporidiosis. In addition, several nondermatophytic fungi and opportunistic bacteria have been isolated from chinchillas, such as *Aspergillus niger*, *Cladosporium spp.*, *Rhizopus spp.*, *Klebsiella pneumoniae*, and *P. aeruginosa*, which might pose a health risk in immunocompromised people.

Uses in Research

Chinchillas are used commonly for auditory research. Their cochlea is similar in shape to that of humans, and their range of hearing is similar. In addition, their large tympanic bullae are surrounded by thin bone that allows easy surgical access to the middle ear, cochlea, and surrounding structures. Chinchillas are also used to study the pathogenesis of and vaccine development for several upper respiratory tract infections, as well as for Chagas disease, atherosclerosis, endocrinology of digestion, thermoregulation, cerebral blood flow, behavior, reproduction, respiratory syncytial virus, and hypothyroidism.

Biodata

Please refer to Table 2.4.

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Table 2.4. Biodata: chinchilla.

Adult body weight: male	400–500 g
Adult body weight: female	400–600 g
Birth weight	40–60 g
Body temperature	37–38 °C (98.6–100.4 °F)
Pulse	200–350 bpm
Respirations	45–80/min
Diploid number	64
Life span	9–18 yr
Food consumption	30–40 g/d; 5.5 g/100 g/d
Water consumption	10–20 mL/d; 8–9 mL/100 g/d
GI transit time	12–15 hr
Breeding onset: male	7–9 mo
Breeding onset: female	4–5 mo
Cycle length	30–50 d
Gestation period	105–120 d; average 112
Postpartum estrus	Fertile
Litter size	2–6
Weaning age (lactation duration)	3–8 wk
Breeding duration	3 yr
Milk composition	7.2% protein, 12.3% fat, 1.7% lactose

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Online Resources for Chinchillas

http://exoticpets.about.com/cs/chinchillas/p/Chinchillas.htm—basic information about chinchillas and their care.
http://www.chincare.com/—care of the chinchilla.
https://www.na3rsc.org/chinchillas—evidence-based refinements for chinchillas.



THE HAMSTER

The Syrian or golden hamster is popular both as a companion and as a research animal. These short-tailed, stocky animals weigh approximately 120 g and are known for their short gestation period, capacious cheek pouches, ability to escape confinement, and periodic pugnacious demeanor, despite their general docility. Unlike rabbits and guinea pigs, hamsters were only recently domesticated and imported as companion animals to North America. The Siberian or Djungarian hamster is also sold as a pet, and several other hamster species are used as animal models in studies that take advantage of unique species characteristics.

Origin and Description

The golden hamster, *Mesocricetus auratus*, is a rodent of the family Muridae and constitutes the majority of the hamsters used in research or kept as companions. Wild golden hamsters occur within a limited range in the Middle East, where destruction of the territory and predation by owls are threatening the species' existence. In the wild, hamsters live independent lives in deep burrows where they may store up to several pounds of grain. Hamsters are nocturnal with short periods of diurnal activity. Most hamsters used in research and sold as companion animals are descended from one male and two to three female littermates that survived capture and domestication in 1930.

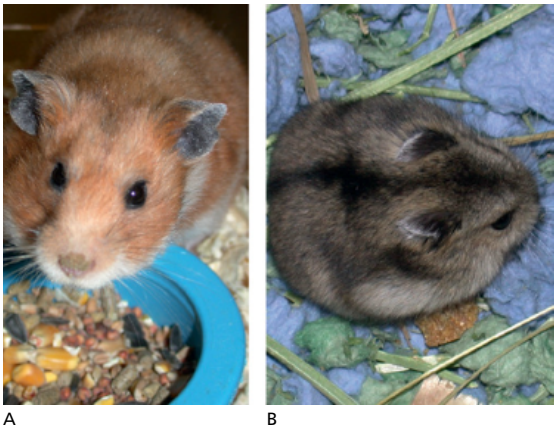
Color varieties of domestic hamsters include a wild-type or reddish-golden brown with a gray ventrum, cinnamon, cream, white, piebald, albino, and the long-haired "teddy bear" variety. Over the past six decades, the number of coat color and pattern mutant genes (e.g., white spotting) encountered in hamster colonies has increased.

Other Hamster Species

Over two dozen species of hamster have been described, but only a small handful of these have been domesticated. Species that are likely to be encountered other than the Syrian hamster (Siberian, Chinese, European, and Armenian) are described briefly below. All other information contained in this section and throughout the remainder of this text refers to the Syrian hamster (Figure 2.60).

The Siberian or Djungarian hamster (*Phodopsus sungorus*), known also as the hairy-footed hamster, is a small (30–50 g), highly social, nocturnal, sometimes aggressive species sold and traded by pet stores and hobbyists. This hamster has a short tail and is gray with a black dorsal stripe (except for a lighter winter coat); a satin variant also exists. Siberian hamsters have cheek pouches, lateral and ventral scent glands, and, unlike the golden hamster, can be housed in family groups. Whereas conspecific conflict occurs less often than in

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A B

FIGURE 2.60. Typical appearance of hamster species, A: Syrian, and B: Chinese.

golden hamsters, interactions with humans may be antagonistic and frequent gentle handling is needed for habituation. Hamsters are highly active and move very quickly, making them skilled at escaping. Male Siberian hamsters are larger than females. Gestation is 18 days long, litter size averages 4 (range 1–9), eyes are open at 10 days, and weaning occurs at 16–18 days. Females mature at 90–130 days, whereas males mature at 150 days. The life span of the Siberian hamster is 9–24 months. These hamsters tolerate cold well, but become heat stressed at ambient temperatures of 34 °C (93 °F). They exhibit daily periods of torpor.

Diseases reported in Siberian hamsters include dermatophytosis, fight-wound abscesses, and neoplasia, especially of the oral cavity, skin, and mammary glands. Weight loss is a common nonspecific sign that accompanies pneumonia, malocclusion, or prolapsed or impacted cheek pouches.

The dark brown Chinese or striped hamster (*Cricetulus griseus*), larger common, black-bellied, or European hamster (*Cricetus cricetus*), and the gray Armenian hamster (*Cricetulus migratorius*) are sold as pets infrequently but have occasionally been used for biomedical research. For example, research on high-altitude physiology, hibernation, and tobacco-related diseases has been performed in these species. Chinese hamster ovaries are used to produce CHO cells, which have been used for *in vitro* cytotoxicity and karyotyping studies. *C. griseus* has also been used as a naturally occurring model for type 1 juvenile-onset diabetes.

The Chinese hamster is gray-brown with a dark stripe down the back (Figure 2.60). Adult males weigh 30–35 g and females slightly less. The females are especially aggressive and must be housed individually. They have cheek pouches and flank glands, and are sexually mature at approximately 90 days of age and continue breeding until 12–15 months of age; life span is approximately 1.5–2 years of age. Litters average 4 offspring, and young are weaned at approximately 21 days of age. Dry nests are necessary for breeding success. Animals are easily stressed, and human interference or other factors can result in reluctance to breed. Chinese hamsters are also prone to dystocia. Tyzzer's disease has been reported as a cause of morbidity.

Anatomic and Physiologic Characteristics

Syrian hamsters have stocky, compact bodies with short legs and tail and small pointed ears. Their skin is very loose, and the normal hair coat is soft and short; however, long-haired varieties ("teddies" or teddy bears) have been bred for the pet trade. Both sexes have flank glands (Figure 2.61), which are usually obscured by hair. These sebaceous glands, which are larger in the male, are used to mark territory, and contribute to pheromone stimuli that determine mating behaviors. The glands reach a maximum size by 21 days in females and 70 days in males, and are a site for conversion of testosterone to dihydrotestosterone. In sexually excited males, the hair over these glands becomes wet.

Adult males can be identified by a relatively long anogenital distance, and when the testicles are in the scrotal sacs, large swellings are visible on either side of the tail, which give their hind end a rounded appearance. Like other rodents, hamsters can withdraw their testicles into the abdominal cavity and uninformed owners sometimes mistake these scrotal swellings for tumors. Mature females have a more pointed hind end and separate urethral and vaginal openings. Hamsters have an average of seven pairs of mammary glands. Adult Syrian hamsters are 14–19 cm (6–8 in) long and weigh between 110 and 140 g with females being larger than males. Their life span ranges from 18 months to 2 years, but older hamsters have been reported. The hamster dental formula is 2(I1/1 C0/0 P0/0 M3/3) = 16, and there is a diastema or gap between the incisors and molars. Similar to other rodents, hamsters are monophydont and have a single set of teeth. Newborn hamsters have fully erupted incisors that function during suckling to strip milk from the teats of the dam. Hamster incisors are open-rooted (i.e., grow continually), and are covered by yellow-orange enamel on the labial side. The lower incisors are much longer than the upper, and may appear loose in



FIGURE 2.61. Flank gland on a Syrian hamster.

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young hamsters due to incomplete ossification and flexibility of the mandibular symphysis. This should not be mistaken for a broken jaw. Unlike guinea pigs and chinchillas, the molars of hamsters and all other myomorph rodents do not grow continuously, so overgrown cheek teeth are not a problem in these species. The incisors are constantly growing, however, and overgrowth can occur, as for many other rodent species (Figure 2.62). The irregular occlusal surface of the molars retains food particles making the teeth prone to cavities if *Streptococcus mutans* is present. Historically, hamsters were useful models for dental disease; however, other rodent models are now more common. The upper lip is divided into two halves by a cleft called the philtrum. Hamsters, like other rodents, are obligate nasal breathers and cannot vomit.

Hamster cheek pouches are oral cavity evaginations that extend between each jaw and cheek to the level of the scapula. These muscular sacs, measuring approximately 35–40 mm × 4–8 mm × 20 mm long, are lined with stratified squamous epithelium and are functionally used to transport food and bedding, and also likely assist with food hoarding (Figure 2.63). Female hamsters may use the pouches to hide their young if they are disturbed or perceive danger. The sacs are thin walled, highly distensible, well vascularized, and devoid of lymphatic tissue other than some minor vasculature. Cheek pouches have been used experimentally to provide an immunologically privileged site for tumor induction and transplantation as they will support the long-term survival of transplanted foreign tissue without immunological rejection. However, this previously important experimental model has largely been replaced by immunodeficient and genetically modified mice.



FIGURE 2.62. Syrian hamster with incisor malocclusion.



FIGURE 2.63. Syrian hamster with cheek pouches distended with food. Courtesy of A.J. Wang.

The stomach of hamsters is separated into glandular and nonglandular areas. The esophagus enters the nonglandular forestomach, which is functionally similar to that of ruminants, and is the site of pregastric microbial fermentation. The hamster stomach normally contains small numbers of yeast and bacteria, such as staphylococci and *Enterobacteria* spp. The duodenum has a descending and ascending loop. The jejunum is approximately 2.5 times the length of the duodenum. A short ileum connects the jejunum to a slightly sacculated cecum, which then connects to the colon. Like rabbits and other rodents, hamsters are coprophagic. The colonic separation mechanism in hamsters is similar to that described for guinea pigs. Soft cecal pellets are taken directly from the anus with the incisors, masticated, and swallowed. The hamster liver has four lobes—right dorsocaudal, left dorsocaudal, dorsal median, and ventral median. The gall bladder is located in a depression of the ventral median liver lobe. The pancreas has three lobes, gastric, splenic, and duodenal.

Hamsters have four digits on the front feet and five digits on the hind feet, each with a small, slightly curved toenail that may require periodic trimming. The heart is located on the midline and contacts the chest wall from ribs three to five. There are two cranial vena cavae and one caudal vena cava. The lung consists of one large left lobe and four right lobes. The trachea bifurcates at the level of the fourth rib.

Adrenal glands in the male hamster are larger than those in the female. The bean-shaped kidneys lie on either side between the second and fourth lumbar vertebrae, with the right one more cranial than the left. Each has a single, long papilla that extends into the ureter. Hamsters produce up to 7 mL of urine per day, and the urine is high in protein and has a high pH (>7.5) as a result of their primarily herbivorous diet. Hamster urine is typically cloudy in appearance because of normal crystalline precipitates. Male hamsters have an os penis. Male accessory sex glands include ampulla glands, seminal vesicles, coagulating glands, bulbourethral glands, and a three-lobed prostrate. The hamster uterus has two horns and a uterine body.

Although Syrian hamsters are not true hibernators, with shortened day length, ambient temperatures less than 8 °C (48 °F), short light cycles, and isolation, pseudohibernation behavior may be observed. Hamsters remain sensitive to touch during this period, though they do exhibit a characteristic "hibernation posture" and have greatly slowed metabolism when in this state. In addition to this characteristic, hamsters can enter a period of deep sleep from which they are not easily

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Table 2.5. Examples of inbred strains of hamsters and their characteristics.

Inbred strain designation	Characteristics
Bio 14.6	Acromelanic white, cardiomyopathy
Bio TO-2	Cardiomyopathy
UM-X7.1	Cardiomyopathy
MHA	White, prone to dental caries
Bio F91 B	Hypercholesterolemia, atherosclerosis
APA	Glomerulosclerosis

aroused. Thus, when presented with an inactive hamster, particularly one that has been housed under cold conditions (i.e., less than 50 °F), the animal should be slowly rewarmed to determine if arousal is possible—even if the animal appears to be dead!

Several inbred hamster strains have been developed using the procedures outlined for mice (see Chapter 1 and Table 2.5 below). Interestingly, outbred hamsters exhibit high levels of genetic similarity in their histocompatibility complex, possibly due to the recent introduction of a small population of genetically related animals as progenitors for all domesticated hamsters. Because of this, Syrian hamsters in pet or laboratory colonies exhibit a high degree of immunologic tolerance to both homografts and heterografts of both normal and neoplastic tissue. This tolerance is even more pronounced in the tissue of the cheek pouch. Hamsters lack suppressor T cells and have atypical cytotoxic T cells.

Hamsters as Companion Animals

Behavior

Hamsters make several vocalizations, and these should always be interpreted in the context within which they are made. Short, high-pitched squeaks can be made when hamsters experience positive excitement, such as hearing the rustling of a food treat bag or when exploring new cage furnishings. Hamsters can also squeak because of fear, frustration, or pain. A nonhabituated hamster may squeak when being picked up because it perceives the situation as being fearful. Again, frequent short, positive handling sessions in which a food treat or gentle petting is given can help hamsters to readily overcome handling fear. Hamsters can make a clicking sound with their teeth when content, but they can also grind their teeth (bruxism) when cold, uncomfortable, or in pain. Concurrent evaluation of body posture and the setting in which the sound is occurring can aid in interpreting whether concern is warranted. Hamsters are fastidious groomers, and any indication of an unkempt hair coat is usually indicative of ill health (Figure 2.64).

Hamsters can be aggressive and territorial toward other hamsters, especially when a female hamster is pregnant or lactating, although progesterone and its metabolites have been shown to inhibit aggression in female hamsters. Most agonistic encounters are preceded by ultrasound communications, which are more pronounced between females, and to the human observer, may appear with no warning. Studies on group-housed hamsters indicate that hamsters may prefer social housing, although such interactions can be stressful, leading to agonistic behavior and obesity. Pairing or social housing of littermates or young, weaned animals helps to ensure more harmonious groups (Figure 2.65). Additionally, ensuring that there are sufficient tunnels or hiding places for all animals can help to reduce agonistic encounters.



FIGURE 2.64. Hamsters are fastidiously groomed and a hamster with an unkempt coat is often an early sign of ill health.



FIGURE 2.65. Male hamsters are readily group housed, particularly when socially grouped prior to sexual maturity.

Life Span

Hamsters have a life span of 18–36 months, with Syrian hamsters having longer lifespans. In commercial situations, female hamsters produce 5–6 large litters during their first 6 months of life, and then produce smaller litters until the dams are

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12–15 months old, after which they may be retired depending upon breeding capacity and objectives. Males are used for commercial breeding until 12 months of age.

Handling and Restraint

Hamsters have a reputation for aggressiveness toward handlers, a characteristic usually exhibited after rough handling or a sudden disturbance. This is thought to be related to the highly nocturnal nature of hamsters, as they sleep deeply during daylight hours and are difficult to arouse compared to other domesticated rodents, for example, rats, mice, and gerbils. Hamsters, even those recently captured in the wild, are tamed readily through gentle and repeated handling (habituation). Hamsters may exhibit agonistic postures and may bite if roughly handled, startled, injured, or abruptly awakened. Hamsters may be picked up in a small container, with a towel, by grasping the large amounts of loose skin of the neck that constitute cheek pouch capacity, or by cupping the hands and gripping over the back (Figures 2.66 and 2.67). A protective glove may be used if the animals are unaccustomed to handling. Gentle deliberate movements, with care taken to arouse a slumbering animal before handling, and the skill and comfort level of the handler are all factors that contribute to successful restraint.

Housing

Hamsters are remarkably adept at chewing through and escaping from their cages. Unlike rats and mice, escaped hamsters will usually not return to their cages. The use of live traps baited with peanut butter or a ramp leading into a container placed against a room wall may be necessary to catch an escaped hamster, although they may live for months hiding in a house. Companion hamsters are often provided with running wheels to alleviate boredom and promote exercise (Figure 2.68). While this provides animals with the opportunity to satisfy roaming behaviors within an enclosed environment, it can be problematic because most running activity occurs at night and may disturb human occupants of the household. This can be significant considering that some hamsters, notably pregnant females, have been reported to run up to 8 km daily. Additional in-cage resources to consider providing include a shelter for hiding (Figure 2.69), boxes to dig and burrow in as well as items composed of nontoxic substances for chewing and exploring and timothy hay.

Hamsters kept for biomedical research are generally housed in plastic, solid-bottom cages with deeply piled cellulose or wood shavings for bedding. For animals weighing greater than 100 g, cages should be 123 $cm^2 \times 15–18$ cm high (ILAR and CCAC guides). More space is needed for breeding females with litters. Ambient temperatures of 18–26 °C and relative humidity between 40% and 70% are well tolerated by hamsters. Hamsters are prodigious tunnel-makers, and prefer bedded, solid-bottom cages to wire-floored cages (Figures 2.68 and 2.70). Given a deep enough cage with abundant substrate, hamsters will create an impressive system of tunnels through the bedding within their cages. Hamsters also create elaborate nests, given the appropriate material, such as crinkle paper, paper towels, or facial tissues. Because hamsters have blunt noses, they may have difficulty eating from slotted sheet metal hoppers or wire mesh feeders if units with small spaces between bars are used. Slots should be more than 1.1 cm wide to allow



A



B

FIGURE 2.66. A. Towel restraint for examination of a hamster.* B. Firm restraint of hamster for dosing, performed by grasping the loose skin around the back and shoulders. *Courtesy of Calgary Avian & Exotic Pet Clinic.

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FIGURE 2.67. A method for scooping a hamster out of its cage is demonstrated.



FIGURE 2.68. Male research hamsters group housed with running wheel, enrichment resources and shoebox-type cage with cellulose bedding.



FIGURE 2.69. Hamsters appreciate having a shelter for resting undisturbed. Courtesy of Calgary Avian & Exotic Pet Clinic.

the hamster to comfortably pull food into the cage. Alternatively, food can be placed on the cage floor.

Hamsters chew plastic, wood, and soft metals and will escape easily from poorly secured or constructed cages. Transport boxes are usually lined with mesh or light metal screening for this reason.

Hamsters produce relatively little odor and less urine than other rodents because of their desert origins. Research colony hamster cages are changed once or twice weekly, except when neonates are present. Cages are sanitized with hot (82 °C or 180 °F) water with or without a detergent or with a nontoxic disinfectant followed by a thorough rinse. Bottles and hoppers are cleaned at the same time as the cages.

Whereas a number of commercial materials are available for bedding substrate, cellulose pellets, aspen shavings, or other hardwood chips are usually preferred, as they allow ample opportunities for burrowing. Soft woods, such as pine and cedar, should be avoided, as these have been associated with dermatologic conditions and respiratory irritation in hamsters, and may induce hepatic enzymes, interfering with research protocols and anesthesia. Shredded newspaper is discouraged as a sole source of bedding, as it is minimally absorptive and contains undesirable pigments and chemicals.

Feeding and Watering

Hamsters are both granivores and insectivores. Although the nutritional requirements have not been determined specifically, a pelleted rodent diet that contains approximately 16% protein and 4–5% fat is typically provided and appears to provide a nutritionally adequate diet. Hamsters eat 8–12 g of feed and drink 8–10 mL of water per 100 g of body weight daily. They eat several small meals approximately 2 hours apart. Protein deficiency may cause alopecia, whereas dietary fat levels exceeding 7–9% may be associated with increased mortality. Vitamin E deficiency in pregnant hamsters may result in fetal death, but shouldn't occur if a balanced rodent pelleted diet is fed. Laboratory rodent feeds may be repackaged in small, unlabeled bags and sold in pet stores without milling and expiry date information. Low-protein but attractively wrapped "treats" may not be adequate diets for growth and reproduction. Seed-based diets are not appropriate, as hamsters will preferentially consume high-fat seeds, creating an unbalanced diet. Seeds can be provided as occasional food treats, though.

Dams with litters should receive their feed directly on the floor, as preoccupation with hopper-bound pellets may result in neglect of the young. Young hamsters begin gnawing solid food and drinking water at 7–10 days of age; therefore, the sipper tube should extend low into the cage but not into the bedding.

Hamsters are coprophagous and consume feces directly from the anus. This behavior occurs many times each day and is thought to be beneficial for ensuring sufficient levels of protein and vitamins are ingested.

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FIGURE 2.70. Typical plastic cage used for housing pet hamsters. A running wheel is provided for enrichment in the large cage and a small nest cage is attached by means of a tunnel to add complexity.

Reproduction

Sexing and Anatomy

Viewed from above, the rear margin of the male hamster is rounded because of the scrotal sacs, and the female posterior is pointed toward the tail (Figures 2.71 and 2.72). Gentle pressure applied to the lower abdomen will cause the testes to protrude into the scrotal sacs. Males have a greater anogenital distance than do females and a pointed genital papilla with a round opening. Male hamsters have prominent, dark marking glands in the skin of both flanks, visible as indentations in the hair coat. These glands may be difficult to see without shaving the animal. Females have 12–17 mammary glands; nipples are readily visible on the adult female but are not seen easily on males.

Breeding Activity

Just as hamsters in the wild have a winter (hibernal) sexual quiescence, laboratory and companion hamsters also have a normal seasonal breeding quiescence in the winter months. During this time, fecundity decreases and litter mortality increases. Provision of a constant temperature (22–24 °C; 73 °F) and 12–14 hours of light reduces some of this effect.

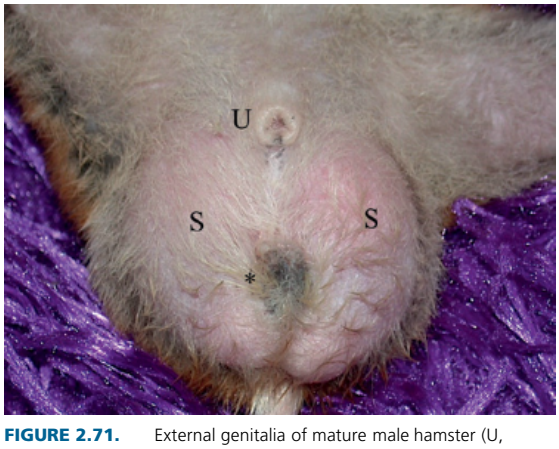


FIGURE 2.71. External genitalia of mature male hamster (U, urethral opening; S, scrotum; *, anus). Courtesy of L. Sereda.



FIGURE 2.72. External genitalia of mature female hamster. UO, urogenital opening; *, anus. Courtesy of A.J. Wang.

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Golden hamsters become sexually mature at 32–42 days, but managed breeding usually is delayed until the female is 6–10 weeks and the male is 10–14 weeks (85–130 g). Hamsters have an estrous cycle lasting approximately 4 days. Postpartum estrus is usually anovulatory, but a fertile estrus follows weaning by 2–18 days. Vaginal pheromones and chemical production (dimethyl disulfide) stimulate aggression and attract males. On the morning after estrus, an opaque, tenacious, odiferous, and stringy vaginal discharge is produced and is referred to as the postovulatory discharge. Presence of this secretion should not be confused with a disease process and can be used to stage the estrous cycle for future breeding.

Except for the few hours of estrus occurring once during the 4-day cycle, a sexually unreceptive female will usually attack a recently introduced male. Females will demonstrate lordosis behavior approximately 8 hours prior to ovulation.

Several breeding schemes can be used. *Hand mating:* When small numbers of animals are being bred, the male can be introduced either directly to the female's cage or on top of a wire lid to gauge female acceptance about 1 hour before the start of the dark cycle. If the female does not attack and displays lordosis, the male is introduced to the cage and then removed from the breeding cage after copulation. *Monogamous pair mating:* A prepubertal male and female are introduced and housed together permanently, assuming they continue to be compatible. Although more males are required with this system than the hand mating scheme, it is labor efficient. During *sequential monogamous mating*, seven females are rotated through a male's cage in a series at weekly intervals, resulting in litter intervals of 35–40 days. After weaning of the litter, the female is returned to the male's cage for 1 week every seventh week. This method is labor efficient but places greater demands on studs if smaller numbers of males are used. *Group or harem mating*: One to five males are placed with a larger number of females. Seven to 12 days after pairing, the pregnant females are removed and housed individually until after pups have been weaned. Fighting may occur when females are returned to the group cage, and additional space provisions, monitoring, and hiding areas are required for this system to be successful.

Pregnancy and Rearing

The absence of postovulatory discharge at 5 and 9 days postmating and the observation of a distended abdomen and rapid weight gain at 10 days are signs of pregnancy. The hamster's gestation period lasts 15–16 days and embryo implantation occurs between days 4 and 6.

Before delivery, the female becomes active and restless and develops a vaginal discharge. Litters contain 5–9 offspring. Infertile matings or crowding of females may produce an occasional pseudopregnancy of 7–13 days in duration. Active nest building may enhance hormonal functions associated with parturition and lactation and is more prodigious when temperatures are cooler. Nest material, such as paper tissues or shredded paper strips, should be provided to pregnant hamsters several days before parturition. Transfer of the nest that contains neonates reduces disturbances that may occur when changing cages. As neonatal hamsters are very immature and require a warm environment, a good quality nest is essential.

Litter abandonment and cannibalism, common during the first pregnancy and the first week postpartum, may occur if the nest is scant, disturbed, or too visible; if the young are born on wire, handled, or bite the mother while nursing; or if the diet is inadequate and the dam does not produce milk. Large or small litter sizes in a noisy environment may also result in abandonment. The female hamster may conceal her newborn litter in her cheek pouches if a threat is perceived, which can result in injury to or suffocation of the offspring. To avoid disturbing the neonates, the female should be supplied with a week's supply of food and bedding 13 days after mating. This allows the mother to nest undisturbed, especially if some feed is placed on the floor of the cage and the water bottle tube can be reached by the young. Hair growth begins at 9 days and weaning occurs at 20–25 days postpartum.

Fostering is less successful with hamsters, as both adopted and natural litters may be cannibalized. Cross-fostering onto dams of other rodent species has not been successful because of the extreme immaturity of hamster young and their sharp incisors. Hand rearing also is not successful.

Disease Prevention

The general husbandry and disease prevention measures mentioned in Chapter 1 should be observed. Common husbandry problems resulting in disease in both laboratory and pet hamsters are fighting, cannibalism of young, escape from cages, susceptibility to climatic changes, and inadvertent food and water deprivation.

Public Health Concerns

LCMV infection has received attention because of several outbreaks in humans, most recently in 2012. In 2015, severe disease and death were recorded in individuals receiving organ donations from a donor with an active LCMV infection associated with a pet hamster. Most pet rodents are purchased from small breeders and redistributed in large centralized centers, allowing infectious agents to spread readily between animals and species. In response to this, the Centers for Disease Control and Prevention (CDC) has increased efforts to eliminate this pathogen from breeding operations selling to wholesale or retail pet suppliers in the US. *Salmonellosis*, *Rodentolepis* (*Hymenolepis*) *nana*, giardiasis, and *Acinetobacter* spp. infections are hamster diseases of potential public health significance, particularly in association with pet hamsters.

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Table 2.6. Biodata: Syrian hamsters.

Adult body weight: male	85–130 g
Adult body weight: female	95–150 g
Birth weight	2 g
Body surface area (cm^2)	11.8 × (weight in g)$^{2/3}$
Body temperature	37–38 °C (98.6–100.4 °F)
Diploid number	44
Life span	18–24 mo
Food consumption	8–12 g/100 g/d
Water consumption	8–10 mL/100 g/d
Breeding onset: male	10–14 wk
Breeding onset: female	6–10 wk
Cycle length	4 d
Gestation period	15–16 d
Postpartum estrus	Infertile; nonovulatory (golden hamster) fertile (Siberian hamster)
Litter size	5–9
Weaning age (lactation duration)	20–25 d
Breeding duration	10–12 mo
Commercial	5–7 litters
Young production (index/female)	3/mo
Milk composition	12.0% fat, 9.0% protein, 3.4% lactose

Acinetobacter spp. infection in humans can lead to osteomyelitis and tenosynovitis, conditions that are difficult to cure. The possibility of rabies occurring in pet or research rodents is extremely unlikely because they are not likely to be exposed to infected animals in the rabies virus cycle. More recently, it has been demonstrated that companion hamsters can be naturally and symptomatically infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may transmit the disease to humans. Owners should always be reminded to wash hands carefully after holding and playing with their pets and to avoid handling these animals when they are sick. Hamsters are banned as companion animals in Hawaii.

Uses in Research

Approximately 181,000 hamsters are used annually in research in the United States, while fewer than 4,000 are used annually in Canada, although these numbers increased substantially during the 2020 SARS CoV-2 pandemic, as hamsters were one of the primary models used. Most hamsters are outbred, but useful inbred strains exist as animal models for epilepsy, muscular dystrophy, and heart failure. Hamsters are used in investigations of congenital anomalies, dental caries, microcirculation, protozoal infections, gerontology, behavior, histocompatibility, infectious diseases, respiratory neoplasia, viral oncogenesis, muscular dystrophy, left-sided atrial thrombosis and ventricular hypertrophy, gallstones, amyloidosis, pancreatic neoplasia, cestodiasis, toxicology, reproductive physiology, circadian rhythms, lipid metabolism, and, in the Chinese hamster, diabetes mellitus. Hamsters are used in various infectious disease studies, as they are relatively susceptible to infection with a wide range of bacterial, viral, and prion diseases. Hamsters are an excellent model for SARS-CoV-2 infection

Biodata

The values listed in Table 2.6 are approximations only and may not represent the normal range in a given population.

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Online Resources for Hamsters

http://exoticpets.about.com/od/hamsters/tp/hamsterguide.htm—choosing and caring for pet hamsters.
http://www.ask-the-vet.com/hamster-care.htm—health information for hamsters.
http://www.hsus.org/pets/pet_care/rabbit_horse_and_other_pet_care/how_to_care_for_hamsters.html—site for hamster care.



THE GERBIL

The Mongolian gerbil or jird is an active, generally easy-to-handle, and nonaggressive rodent distinguished by its monogamous mating behavior, water and temperature conservation mechanisms, spontaneous epileptiform seizures, ease of tail degloving, and relative freedom from other spontaneous diseases.

Origin and Description

The Mongolian gerbil, *Meriones unguiculatus*, is a rodent of the family Muridae. There are 14 genera and 110 species of gerbil-like rodents within the subfamily Gerbillinae, and all are characterized by movement via jumping or hopping actions. Although species other than the Mongolian gerbil are rarely used as research subjects in North America, in other countries *M. libycus*, *M. shawii*, and *M. tristami* continue to be used as research models.

The Mongolian gerbil is native to desert regions of Mongolia and northeastern China, and is an active, curious, burrowing, social animal with cycles of activity, feeding, and rest during day and night, although in captivity peak activity may occur in the middle of the dark cycle. They consume equal amounts of food day and night. In the wild, gerbils are diurnal with crepuscular tendencies and may hibernate. Their burrows are elaborate tunnels with multiple entrances, nesting rooms, and food chambers for storing seeds over the winter. Social groups of gerbils may include 10–20 entrances, and in the wild, gerbils remain near an entrance. Gerbils retain a "mental map" of their burrows and when threatened by a predator bolt to the most accessible hole.

All Mongolian gerbils used for research in North America came from 20 breeding pairs that were originally trapped in Mongolia and taken to Japan. Of these, four breeding pairs were sent to the United States in 1954 to the laboratory of Dr. Viktor Schwentker, who established the first commercial breeding colony. Most laboratory gerbils today are highly related, making gene mapping studies with this species difficult because of the low allelic polymorphisms that are typically used to map genes.

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FIGURE 2.73. Agouti gerbils (left) courtesy of Phyllis Paterson are most common, but solid coat colors with white markings are also seen. Middle image courtesy of Calgary Avian & Exotic Pet Clinic.

The agouti or banded brown-haired Mongolian gerbil is the color variety sold commonly as companion or research animals, but gerbils with over 20 different hair coat colors are available (Figure 2.73). The agouti coloration is the dominant color pattern. Black gerbils frequently have a white stripe or patch that extends from the chin to the chest and white spots on the feet. White, dove, piebald, and cinnamon color mutations exist as well as a hairless mutation.

Anatomic and Physiologic Characteristics

Gerbils have large, slightly bulging black eyes, prominent whiskers, and often sit upright due to their elongated hind limbs which are adapted for hopping. Gerbils of both sexes have a distinct midventral abdominal pad, which is larger in males, and is composed of large sebaceous glands under control of sex hormones. Secretions from this gland are used in territorial marking and pup identification. Both sexes mark by sliding on the belly or rubbing the abdomen against surfaces, but males mark more frequently, especially if raised in a naturalistic environment or with reproductively active females. The female gerbil has four pairs of teats, two thoracic and two inguinal. Spontaneous, convulsive (epileptiform) seizures occur in approximately 30% of companion or laboratory gerbils. These seizures, which begin at approximately 2 months of age, may be hereditary. The seizures range from mild to severe and can be induced by various stressors such as unfamiliar surroundings or loud noises.

Grooming using normal red-tinged protoporphyrin and lipid secretions from the Harderian gland and saliva may provide means of chemical communication and pelage insulation. In addition, Harderian gland secretions provide lubrication to the eye and are thought to be photoprotective. Accumulation of porphyrin secretions around the eyes or nose is frequently an indication of stress or poor health.

Gerbils exhibit lipemia more frequently than other rodent species. The lipemia is probably of dietary origin and is accentuated by feeding high-fat feed or sunflower seeds. Gerbils appear to develop lipemia even on diets with standard fat levels (4–6%). High serum cholesterol levels, for example, 41.1 mmol/L (1,590 mg/dL), have resulted from feeding gerbils standard rodent diets plus 1% cholesterol. Hypercholesterolemia is associated primarily with low-density lipoproteins. Hepatic lipidosis and gallstones, but not atherosclerosis, develop in gerbils maintained on a high-fat diet. A gall bladder is present in gerbils. Like other rodents, gerbils have a large cecum and colon. The cecum weighs 3–5% of the body weight. The small intestine is longer than in more herbivorous rodents, with the small intestine being 48% and the large intestine 40% of the total intestinal length. Gerbils have the ability to lengthen the GI tract in response to increased dietary fiber. Like rabbits and other rodents, gerbils are coprophagic.

Similar to other rodent species, there is some sexual dimorphism in gerbil erythrocyte parameters. Compared with female gerbils, males have higher packed red cell volumes, hemoglobin levels, total leukocyte counts, and circulating lymphocyte counts. Some erythrocytes of both sexes have prominent polychromasia and basophilic stippling. As for guinea pigs, hamsters, and rabbits, in gerbils the neutrophils are termed heterophils because they are seen to contain eosinophilic cytoplasmic granules with Romanowsky (Wright's) stains.

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Compared with other rodents, gerbils have a higher adrenal gland weight: body weight ratio, which may contribute to their unique water-conserving capability. They have developed adaptive mechanisms for temperature extremes, such as spreading saliva on their pelage to promote evaporative heat loss. The thymus is within the thorax and persists in adults, as in rats and mice. The body weight of gerbils varies from animal to animal and among colonies, ranging from 50–80 g for females and 80–130 g for males. Although such variability may be a genetic phenomenon, diet is a likely major contributing factor, that is, higher fat content and diets of better nutritional quality lead to heavier body weights. The hind legs of gerbils are adapted for jumping and are elongated and very muscular with four clawed toes on large furry feet. The forefeet are relatively small with five clawed toes that are used to hold food during eating. The soles of the hind feet are covered with fur, making climbing difficult.

Gerbils as Companion Animals

Behavior

Gerbils are clean, friendly, curious, and quiet, produce little waste and odor, rarely bite or fight, and adapt to gentle handling easily. Gerbils communicate with each other via chirps and ultrasonic vocalizations and can make a soft purring sound when content. High-pitched squeaking may be an indication of fear or pain and may also be a precursor to fighting with other gerbils. Gerbils are more exploratory and less thigmotaxic than other small rodents. An escaped gerbil prefers an open space or its cage to hiding, although escaped gerbils may be difficult to capture. Gerbils rarely vocalize but often sit upright, or when threatened or excited, drum their rear legs on the floor ("thumping").

Although gerbils are social animals that live in either mixed or same-sex groups, they can be aggressive toward intruders. Gerbils may fight if crowded or mixed as adults, but the usual social interactions are grooming, wrestling, and communal sleeping. Incessant digging with the forepaws in the corners of the cage is a characteristic of gerbils and may be an indication of a stereotypic behavior due to lack of appropriate environmental stimulation. Similarly, gnawing at the cage bars and pacing may be signs of boredom suggesting that the environment is inadequate. Old gerbils or gerbils that are experiencing pain are more inclined to bite than are young or breeding adults.

Pain may be difficult to detect in gerbils because they are prey species. Close observation for subtle behavioral changes is necessary to detect distress or states of disease. Piloerection, hunched posture, reduced locomotion, reduced food consumption and feces production, and lack of interaction with cagemates may all be indicators of poor health or pain.

Gerbils paired after reaching puberty (10 weeks) or reunited after prolonged separation may fight. Fighting is reduced if the gerbils reach maturity in the same cage or if the animals are allowed to recover simultaneously from anesthesia in a neutral cage. It may not be possible to mix adults from different established pairs without serious fighting. Agouti female gerbils prefer agouti mates, whereas sandy and black females prefer non-agouti mates.

Other behavioral characteristics of gerbils are their stable monogamous matings, rapid learning of avoidance responses but poor maze performances (perhaps because they are too curious), and epileptiform seizures in some gerbils older than 2 months after excitement, sudden noise, handling, or introduction to a strange environment.

Life Span

The reproductive life of a female gerbil ranges from 15 to 20 months, during which time 4–10 litters may be produced. The average life span is 3 years, but 4-year-old gerbils are common.

Handling and Restraint

Gerbils can be readily habituated to gentle handling from a young age. They are best picked up from their enclosure by scooping from underneath using one or both hands. Once out of their enclosure, for a closer examination, the gerbil can be grasped firmly at the base of the tail and the neck at the nape; the animal is then lifted and cradled in the hand. The tail is long and relatively inflexible. Extreme care must be taken not to pull on the tail because the skin on the caudal tail comes off readily (degloving injury or "tailslip"). The gerbil may be restrained more securely with an over-the-back grip (Figures 2.74 and 2.75). Gerbils resist being placed on their backs and, while struggling, may be dropped accidentally, especially by small children or those unaccustomed to handling rodents. An immobility response is elicited readily by grasping the nape of the neck.



FIGURE 2.74. Once out of its enclosure, a gerbil can be held in the hand with a firm grasp on the base of the tail.

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Housing

Plastic or metal rodent cages with a solid floor and deep bedding are the usual housing arrangement and are preferred to wire cages without bedding (Figure 2.76). Bedding should be of sufficient depth (at least 2 cm) to facilitate nest building and digging, and should be clean, dry, absorbent, and nonabrasive. Provision of an opaque cage, material for nest building, and a shelter or hiding place within the cage may improve reproductive and maternal performance (Figure 2.77). Gerbils are active gnawers and burrowers, and cages should be designed to prevent escape. In-cage resources may include running wheels, items to chew, a digging or burrowing box, and nesting materials, such as crinkle paper strips. Companion or laboratory gerbils exposed to a naturalistic environment (stones, sand, water dish) find food more readily, rear up, mark, and move more often than do controls. Similar to chinchillas, access to a dust bath assists with grooming (Figure 2.78).

Current US guide requirements suggest that mature gerbils older than 12 weeks require a floor area of 230 cm^2 (36 in^2) per animal. A breeding pair requires a cage area of 1,300 cm^2 (180 in^2). Cage sides should be at least 15 cm (6 in) high. Cages suitable for rats and hamsters may be satisfactory for gerbils, although they may not provide enough room for gerbils to perform normal hopping or jumping actions.



FIGURE 2.75. An "over the back" grip for a gerbil.



FIGURE 2.76. Two examples of suitable housing and resources for gerbils. Animals can dig, shelter, build nests, and perform a range of behaviors. Running wheels can be added for additional exercise. Courtesy of Calgary Avian & Exotic Pet Clinic.



FIGURE 2.77. A naturalistic shelter used to provide a hiding place for gerbils within the cage.

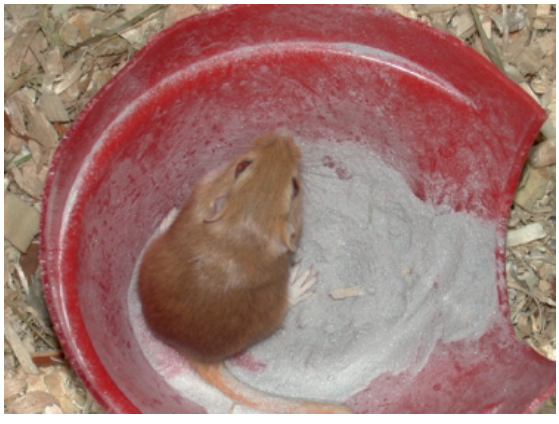


FIGURE 2.78. A sand bath will assist with grooming and maintaining the pelage in good condition. Sand or dust for bathing is available commercially for gerbils.

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Gerbils tolerate a range of temperatures, but they become uncomfortable at temperatures above 35 °C. They possess greater capacity for heat regulation than do many other rodents because of their desert origin. Their tolerance of heat decreases as humidity increases. In the wild, their habitat of deep burrows provides a cool respite against the higher humidity and temperatures experienced in the summer. Gerbils are usually housed at temperatures between 18 and 29 °C (65–85 °F) with a temperature at 22 °C (72 °F) accepted as a compromise. The environmental relative humidity should be above 30%, but at approximately 50% R.H. or higher, the gerbil's hair coat becomes roughened and damp. A 12 : 12 hour light : dark cycle is the usual light cycle for laboratory housing.

Gerbils have efficient urine-concentrating abilities, producing two to four drops of urine every 24 hours, and fecal pellets are small, dry, and hard. In gerbil colonies, the bedding is usually changed when dirty or every 1–2 weeks. Nests of lactating females should be disturbed as little as possible to minimize cannibalism. Nests may be transferred intact to new clean cages. Cages should be washed with hot water and detergent, disinfected, and rinsed.

Feeding and Watering

Gerbils are granivorous or herbivorous and may be fed ad libitum using a food hopper. Gerbils should be fed a complete, freshly milled, pelleted rodent chow containing approximately 16–22% protein. Young begin eating at approximately 15 days of age. Mortality ensues when food in hoppers or water is inaccessible; therefore, supplementary food provided on the cage floor may be necessary for younger animals and food is often provided in J hoppers for ease of access. Quality hamster and gerbil pelleted feeds (not seeds only) are usually available in pet stores. Adult gerbils consume 5–8 g of feed daily. Females display more food-hoarding behavior than do males.

Gerbils may prefer sunflower seeds to pelleted chows, but such seeds, with low-calcium and high-fat content, are not a complete diet. Gerbils 2–5 weeks old may have difficulty opening the sunflower seeds or gnawing the hard pellets, so the pellets should be softened by presoaking in water. Although gerbils in the wild feed on seeds and succulents and require little water, gerbils that are water deprived stabilize at approximately 86% of hydrated weight.

Caged gerbils should be supplied continuously with clean water. Inadequate water consumption may result in infertility, reduced body weight, and death secondary to dehydration. Although gerbils maintain weight when receiving as little as 2 mL of water daily, adult gerbils will consume approximately 4–10 mL daily. Older males drink more water than do females or younger males. Sipper tubes should reach to and be usable by the smallest cage inhabitant. Increased drinking behavior in gerbils may be an indication of disease, for example, chronic renal failure.

Reproduction

Sexing

Weanling and older males have a dark scrotum, and the anogenital distance is substantially greater in males (10 mm) than in females (5 mm), which makes sexing relatively straightforward (Figures 2.79 and 2.80). Both sexes have a genital papilla. The midventral marking (sebaceous) or scent gland is androgen-sensitive and approximately twice as large in the male.



FIGURE 2.79. External genitalia of an 11 day-old female (left) and male (right) pup. The distance between the urogenital papilla and the anus (black bar) is longer in the male even at this age. Nipples are clearly visible on the ventral abdomen of the female pup but not on the male pup. As for many rodent species, pups are born hairless and begin to develop a hair coat between 10 and 14 days. Courtesy of Leah Frei.

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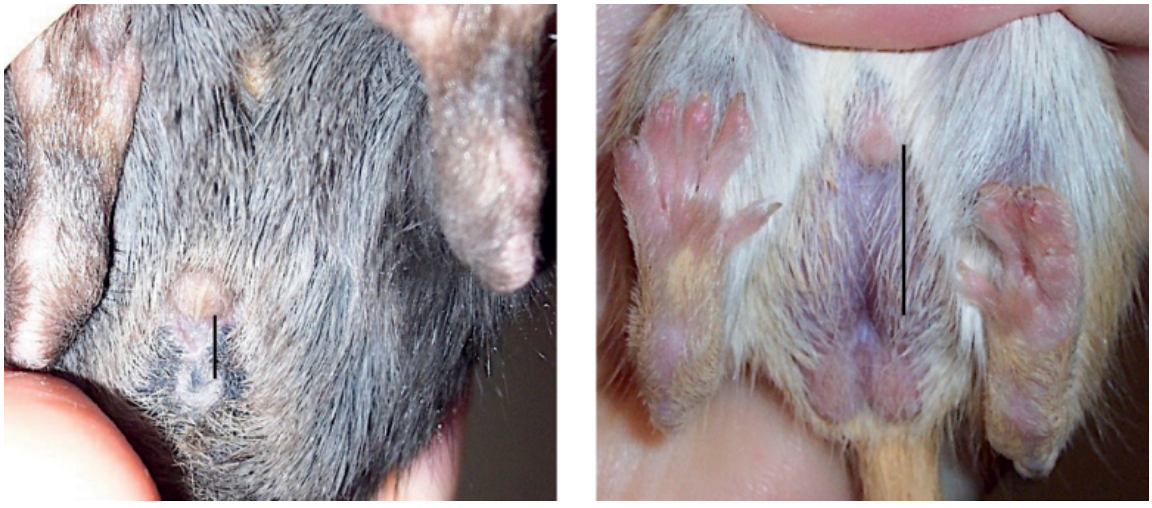


FIGURE 2.80. External genitalia of an adult female (left) and adult male (right) gerbil. The anogenital distance (black bar) is much longer for the male, compared with the female. Scrotal sacs are also present in the male. Courtesy of Leah Frei.

Estrous Cycle

Gerbils are nonseasonally polyestrous, spontaneous ovulators, and generally breed throughout the year. They are mated at 10–12 weeks of age when they weigh approximately 55–70 g; however, the testes may descend and the vagina may open as early as 28 and 40 days, respectively. Because gerbils are often permanently paired, the detection of estrus is rarely a factor in breeding.

The gerbil's estrous cycle lasts 4–6 days, and a fertile, postpartum estrus occurs within 18 hours of parturition in approximately 60% of gerbils. As a rule, the gestation period of lactating gerbils is increased by up to 2 days for each young nursed. Estrus lasts approximately 24 hours, and gerbils in estrus are restless and may have a congested vulva. Estrus may be induced by gentle vaginal stimulation or by pairing adult males and females.

Breeding Programs

Gerbils breed readily in the home or research environment. Breeding pairs established before sexual maturity, at approximately 7–8 weeks of age, are usually stable, monogamous, lifelong arrangements in which one partner's removal or death may render the other sexually and socially incompatible in subsequent pairings or may induce pregnancy failure. The affiliative behavior within pairs may be due to discrimination of a mate's urine odor, although initial pair formation may be determined by pheromones in parotid gland saliva.

The male participates in the care of young and is left in the cage at all times. Separation of breeding pairs should follow fighting, rejection, or aggression toward the young. Some breeders remove the male gerbil for 2 weeks postpartum to eliminate postpartum mating and reduce disturbance of the female and young. The 2-week period should not be lengthened because of the increased potential for fighting when they are reunited. Polygamous (trio) harem groups have been used successfully, but fighting may result.

Pregnancy and Rearing

During pregnancy a mature gerbil will gain between 10 and 30 g. The gestation period of nonlactating gerbils lasts 24–26 days, although both shorter (19–21 days) and longer periods have been reported. Use of the postpartum estrus will lead to concomitant pregnancy and lactation, a situation that leads to delayed implantation and therefore prolonged gestation. In this case, gestation may be as long as 48 days.

Nest-building behavior occurs in both pregnant and nonpregnant gerbils. This activity is accentuated in cooler temperatures. Nests may be constructed from a variety of materials such as paper, cardboard, wooden wool, or commercial nesting materials, which gerbils are adept at shredding. Maternal nests are often covered. A hardwood box, ceramic container, or plastic tube or igloo placed in the cage facilitates nest building.

Usually 3–7 (1–12) gerbils are born per litter, and delivery is almost always at night. Neonates weigh approximately 2.5–3 g at birth and are altricial (naked with sealed eyes and ears). Neonates from small litters tend to weigh more than those from large litters. Ears open in approximately 5 days, hair appears in 6 days, incisors erupt in 12–14 days, and eyes open in 16–17 days. If the litter dies and lactation ceases, the female will resume cycling.

Young rarely are abandoned or cannibalized. Factors that contribute to abandonment include small litters (three or fewer young), excessive handling of the young, lack of nesting material, and cages without provision for hiding. Fostering is possible if the orphaned and host litters are born within a few

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Table 2.7. Biodata: gerbils.

Adult body weight: male	80–130 g
Adult body weight: female	55–85 g
Birth weight (depends on litter size)	2.5–3.0 g
Blood volume	7.7 mL/100 g
Body surface area (cm^2)	10.5 × (weight in grams)$^{2/3}$
Body temperature	37.0–38.5 °C (98.6–101.3 °F)
Diploid number	44
Life span	3–4 yr
Food consumption	5–8 g/100 g/d
Water consumption	4–7 mL/100 g/d
Vaginal opening	41 d or 28 g
Breeding onset: male	70–85 d
Breeding onset: female	65–85 d
Estrous cycle length	4–6 d
Gestation period (nonlactating)	24–26 d
Gestation period (concurrent lactation)	27–48 d
Postpartum estrus	Fertile
Litter size	3–7; 5 average
Weaning age	20–26 d
Breeding duration	12–17 mo
Commercial	4–10 litters
Litters/year	7 avg
Young production	>l/wk per breeding pair

days of each other. Hand feeding of neonatal rodents is difficult, usually because animals cannot be fed frequently enough. This results in overfeeding and subsequent regurgitation and aspiration of stomach content.

Disease Prevention

General husbandry practices to minimize and prevent disease are listed in Chapter 1. Gerbils' fondness for sunflower seeds can produce the false impression of good dietary habits; however, sunflower seeds are high in fat, low in calcium, and are not a complete diet for rodents.

Public Health Concerns

Gerbils in captivity have few spontaneous diseases and even fewer diseases of public health significance. *Salmonella* spp. and *Rodentolepis/Hymenolepis* spp. infections are potential health problems for humans. Both conditions are rare in gerbil colonies. Gerbils could become feral in North America and cause extensive damage to crops, and it is illegal to breed, own, or sell gerbils as pets in California and Hawaii.

Uses in Research

It is difficult to gauge how many gerbils are used in research annually in the United States or Canada, as gerbils are lumped together as "other rodent species" in annual audit reports. Typical research use is thought to be less than 3,000/year in the United States Studies in which gerbils are used include cerebral infarction and stroke, hepatitis E infections, auditory phenomena, parasite infections, epilepsy, infectious diseases, histocompatibility, dental disease, behavior, radiobiology, endocrinology, water conservation, and lipid metabolism. Gerbils are more resistant to radiation exposure than are other laboratory rodents. Cerebral ischemia and infarction can be produced in gerbils through unilateral carotid ligation, and this technique is frequently used for surgical modeling of stroke. In such animals, the posterior communicating artery is ligated, and because the right and left cerebral vascular supplies are poorly connected, an ipsilateral stroke syndrome may be produced.

Biodata

The values listed in Table 2.7 are approximations only and may not represent the normal range in a given population.

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Online Resources for Gerbils

https://www.agsgerbils.org/manualcare—The American Gerbil Society.
http://www.aspca.org/pet-care/small-pet-care/gerbil-care.html—basics of gerbil care.



THE MOUSE

Commensal and wild mice have spread around the world, and the domesticated research or house mouse is kept occasionally as a companion animal. Because mice are small prolific breeders that are easily and economically maintained in large populations, possess great genetic diversity, can be readily manipulated genetically, and are well characterized anatomically and physiologically, they are the most widely used mammal in biomedical research today. Because of intensive study by scientists and common use in research colonies, more is known about mouse biology and disease than most other nonhuman species. Mice are also reared as companion animals and for show by fanciers, and for production of feed sources for reptile and raptor colonies.

Origin and Description

The mouse, *Mus musculus*, is a rodent (order Rodentia) of the family Muridae. In recent times ancestors of these mice spread worldwide from a presumed origin in temperate Asia stretching from modern-day Turkey to China, probably interbreeding with closely related species along the way. Mice can live permanently caged and managed by humans for generations, commensally in human habitations, or entirely in the wild. Wild mice undergo periodic population expansions, and at all times they may cause extensive damage to human food supplies and directly or indirectly transmit infectious diseases to people.

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The domestication and breeding of mice by fanciers led to the genetic diversity of mouse populations that are seen today and to increasing research interest of scientists in the nineteenth century. The long-established Swiss albino or CD-1 mouse became the source of many outbred, white laboratory stocks, although there are several other origins for both white and pigmented mice. Several genera of wild mice other than *Mus* are encountered in research colonies, including field mice, *Microtus* spp.; grasshopper mice, *Onychomys* spp.; cane mice, *Zygodontomys* spp.; and white-footed mice, *Peromyscus* spp.

Pygmy Mice

Pygmy mice, *Mus minutoides*, are the smallest members of the *Mus* family, originate in sub-Saharan Africa, and in recent years have become a trendy small mammal pet. They weigh approximately 1 g at birth and up to 12 g as adults. Their color is blackish brown to red with bellies of white, buff, or gray. They are nocturnal, breed year round, and have litters of 1–5 after a 20-day gestation. Both parents raise the young and sexual maturity occurs at 10 weeks. These mice do well in captivity, even in groups.

Research mice, as well as other research animals, may be conveniently classified into two broad categories based on host microbiology and genetic characteristics. The microbiological classification includes (1) germ-free (axenic) mice, which are free from detectable microorganisms; (2) defined flora (gnotobiotic) mice, which possess a specified flora and fauna; (3) SPF mice, which are free of specified viral, bacterial, and parasitic microorganisms; and (4) conventional mice, which include almost all other mice housed under a variety of conditions.

Genetic classification includes (1) outbred mice, derived from mating unrelated mice, referred to as stocks; (2) inbred mice, genetically homogeneous descendants of at least 20 consecutive brother–sister matings, referred to as strains; (3) Fl hybrids, the first generation produced after mating mice of two different inbred strains; and (4) genetically engineered or modified mice. It is not the intent of this book to discuss the myriad ways in which genetically modified mice may be produced; however, a number of recent references have been published on this subject.

The development of successful genetic engineering techniques for mice over 30 years ago, combined with the high fertility, fecundity, and ease of housing, has together led to the contemporary dominance of this species in biomedical research. The ability to compare genetic similarity between humans and another mammalian species has been an extremely useful tool to study gene function, interactions, disease, and evolution. A complete sequence of the mouse genome was produced in 2002, with more recent work focusing on genetic polymorphisms between inbred strains and specific gene function (http://www.informatics.jax.org).

Several inbreeding schemes exist, and brother–sister mating schemes in each successive generation tend to maximize the speed at which genetic differences (heterozygosity) are eliminated in a new strain. In general, at least 20 brother–sister matings are required to produce a new inbred strain. Genetic mapping of microsatellite markers can be used to select the animals with the genetic traits of interest, which can sometimes reduce the number of matings required for producing inbred strains. Because random mutations will occur spontaneously with time, strains maintained away from the original breeding colony will diverge genetically from the original colony over time and become sublines. This is particularly true if mice are separated before 60 generations of backcrossing.

Selective breeding and inbreeding have produced the diversity of mice encountered today as companion and research animals, with over 450 recognized inbred strains of mice. Because of this enormous variety, in addition to the thousands of genetically engineered strains, it is critical that new strains of mice be named according to conventional nomenclature rules to allow veterinarians and scientists to communicate effectively about mouse strains at a global level.

Inbreeding of mice has resulted in a variety of attractive, strain-specific coat colors. These different inbred variants can possess less desirable genetic predispositions, including tendencies toward immunodegenerative diseases and increased tumor incidence. Regardless of their use, such mice often develop complex abnormalities characteristic of the parent strains. This diversity in disease profiles among strains presents the investigator, animal facility manager, and small animal practitioner with multiple differential diagnostic challenges.

Anatomic and Physiologic Characteristics

The conventional, outbred white mouse is distinguished by its small size and the physiologic accommodations necessary for that size. The rapid heart rate (500–600 bpm), high oxygen consumption (1.7 mL O_2/g/hr), and extraordinary fecundity (potentially one million descendants after 425 days) are notable mouse characteristics.

More than a hundred years of inbreeding and strain development have produced a considerable reservoir of strain variations (Figure 2.81) and mutants, which are used by the millions in the investigation of a vast array of normal and abnormal phenomena. The following characteristics provide a small sample of available mutants: anemic, athymic, bent tail, diabetic, frizzy, fuzzy, grizzled, jolting, naked, nervous, radiation sensitive, and tottering. A wide variety of spontaneous neoplasms occur in inbred strains, listings of which can be obtained from the Mouse Tumor Biology Database (http://tumor.informatics.jax.org/mtbwi/index.do).

Some anatomic characteristics of mice include sexual dimorphism in splenic size (50% larger in males than in females); inability to vomit; a lack of deciduous dentition and presence of open-rooted incisors, which can become overgrown (Figure 2.82 and 2.83); three pairs of thoracic mammary glands and two pairs of inguinal, all reaching from the ventral midline over the flank, thorax, and portions of the

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A B C

FIGURE 2.81. Numerous mouse strain variations exist with a variety of coat color patterns as well as hairless strains. Depicted are a C57BL/6 mouse (A), a nude mouse (B), and a Swiss mouse (C).



FIGURE 2.82. Normal mouse incisors. Note the relative lengths of the maxillary and mandibular incisors.



FIGURE 2.83. Abnormal and overgrown incisors in a pair of mice. When breeding mice, parents who give birth to pups with incisor malocclusions should not be rebred.

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neck; a stomach divided into squamous nonglandular and glandular portions; and inguinal canals that remain open for the life of the male.

Mice as Companion Animals

Behavior

Because of their small size and rapid movements, mice are not suitable pets for small children, but if gently handled, they can become good, albeit small pets for the older child or adult. Mice are timid, social, omnivorous, territorial, and escape-prone rodents that may be housed in smaller spaces and require relatively small quantities of food and water. Mice communicate via audible and ultrasonic vocalizations, the latter occurring more frequently between dams and offspring or between sexually mature adult males and females. Ultrasonic vocalizations occur in predictable patterns, similar to song in bird species, and ultimately shape behavior of socially reared animals. Mice will make high pitched squeaks when in pain or when they sense danger or are fearful and some mice are more vocal than others and will make quieter squeaks when they explore their environment. High-pitched and continuous squeaking should spur immediate and close investigation to ensure that animals are not in danger, embroiled in severe fighting, or in pain.

Although wild mice are distinctly nocturnal, laboratory mice and companion mice are active and resting alternately throughout the day and night. In the wild, mice live in compatible, single male–dominated groups, called demes. The size and complexity of these social structures and the degree to which neighboring demes overlap are highly dependent on the availability of food supplies.

Adult mice, especially males or those previously housed alone, which are newly mixed in the same cage, usually barber one another or fight, as do those existing in unstable hierarchies (Figure 2.84). The hierarchical status in a cage can often be determined from the number and severity of bite wounds over the rump and back (Figure 2.85). Adult male mice, particularly those from different litters, often need to be housed separately to prevent fighting and the resulting abscesses, dermatitis, septicemia, and death. This male aggression is influenced by both testosterone and training, and both innate and learned components are necessary for the full demonstration of aggression. Intermale aggression can be avoided or reduced by early castration, by keeping male littermates together post weaning, by minimizing removal or addition of animals once stable groups have been formed, by moving the old nest to the new cage during cage cleaning, and by ensuring that animals have sufficient space and in-cage resources to be able to escape from agonistic encounters. Mouse urine odor is determined by both genetics and environment and is strain-specific. Female mice seldom fight, but may do so to defend their nests. Mice housed alone tend to be more aggressive toward intruders than their group-housed counterparts. If roughly handled or startled, mice will bite or pinch with their teeth. Barbering or hair chewing is a learned behavior that when seen generally indicates inappropriate housing or social groupings or inadequate in-cage resources. The mouse doing the barbering in a cage is not necessarily the most dominant mouse, and barbering patterns may be strain-specific.



FIGURE 2.84. Moderate barbering seen in a cage of black (C57BL/6) mice. Although barbering doesn't generally harm the affected animals, it may be indicative of a problem within the social group.

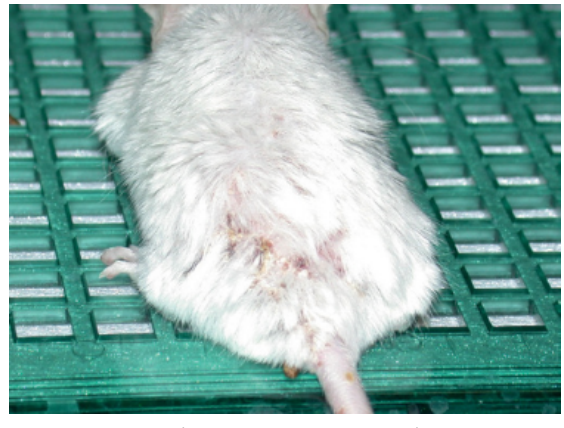


FIGURE 2.85. Fighting injury seen in a CD-1 male mouse.

Life Span

Mice may live 2–3 years, but there are major differences in longevity among strains, owing mainly to differential tumor and disease susceptibilities. For example, AKR (white) and OH (agouti) mice live shorter lives than do A (white) and C57BL (black) strains. Pet mice are typically not inbred, and thus life span and disease susceptibility are more difficult to predict. The breeding life of female mice is approximately 8 months and they can produce 6–10 litters during this period, although few inbred strains will produce more than five litters in a lifetime.

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Handling and Restraint

A significant body of evidence accrued over the past decade has demonstrated that mice should be picked up, and, indeed, prefer to be picked up from their home enclosure using nonaversive or low stress handling methods, whenever possible (Figure 2.86). As depicted, this can be done with a tunnel or other piece of cage furnishing or by gently cupping the body of the mouse with one or both hands. If closer inspection or manipulation is needed, the mouse can be set on a nonslip surface and the grip changed to grasp the animal by the scruff of the neck by thumb and forefinger and inverted, and then the tail held between the palm and little finger (Figure 2.87). Because this standard immobilizing restraint (which creates a dorsal longitudinal fold of skin resulting in a crease on the ventral neck) can be associated with a vagally mediated reflex bradycardia, other methods of firm restraint may be employed, such as light or three-finger restraint (which creates a dorsal transverse fold of skin). Grasping and pulling the tip of the tail may strip the skin from the tail ("tailslip"). Mice can also be scooped up using a small plastic container, and tared plastic containers are convenient for weighing (Figure 2.88).

Housing

Mice kept for research or as companions are usually housed in either solid-sided plastic or plastic-coated wire cages with solid bottoms with wire mesh or slotted bar tops (Figure 2.89). A homemade shoebox cage with a hardware cloth top is satisfactory for pet mice, as are the several wire and plastic cages available in pet stores. Large mice may have difficulty eating through 0.65 cm (1/4 in) mesh, and weanling mice may escape through larger meshes. Care should be taken to select housing materials and surfaces that will prevent escape, loss of young, and fractured limbs.

According to the eighth edition of the ILAR Guide, mouse cages should provide at least 97 cm^2 (15 in^2) floor space per adult (>25 g) mouse, 330 cm^2 (51 in^2) for a dam with a litter, and be at least 13 cm (5 in) high. The CCAC recommends at least 330 cm^2 (25 in^2) as the minimum cage size with 100 cm^2 by 13 cm high per adult mouse and 500 cm^2 for dams with litters. Thus, for group sizes of four to five adult mice the cage area provided should be approximately 400–500 cm^2.

Both bedding and nesting materials are mandatory elements in the mouse microenvironment. Preferred bedding substrates include cellulose pellets or chips and hardwood chips, shavings, or sawdust and they should be hypoallergenic, dust-free, inedible, absorbent (but not cause dehydration of newborn mice), nontoxic, and free of pathogenic organisms. For laboratory mice, husbandry practices may include the use of autoclaved or irradiated feed and bedding to prevent fomite transmission of infectious agents. Softwoods, such as pine and cedar wood shavings, are sometimes used for companion rodent bedding because of their pleasant aroma and low cost. Because volatile hydrocarbons from these shavings may stimulate hepatic microsomal enzymes and may induce dermatitis and nasal irritation and sneezing, they should be avoided as a bedding material for research animals or kiln dried at high temperatures prior to use, which evaporates the volatile oils. Wood wool, paper towels, and commercial cotton nesting materials make excellent rodent nesting material. Complexity can be added to cages through the use of hardwood blocks or tunnels, plastic, wood or paper tunnels, huts, or igloos, small nylon chew toys, and running wheels (Figures 2.90 and 2.91). It is common for different strains of mice to use resources in different

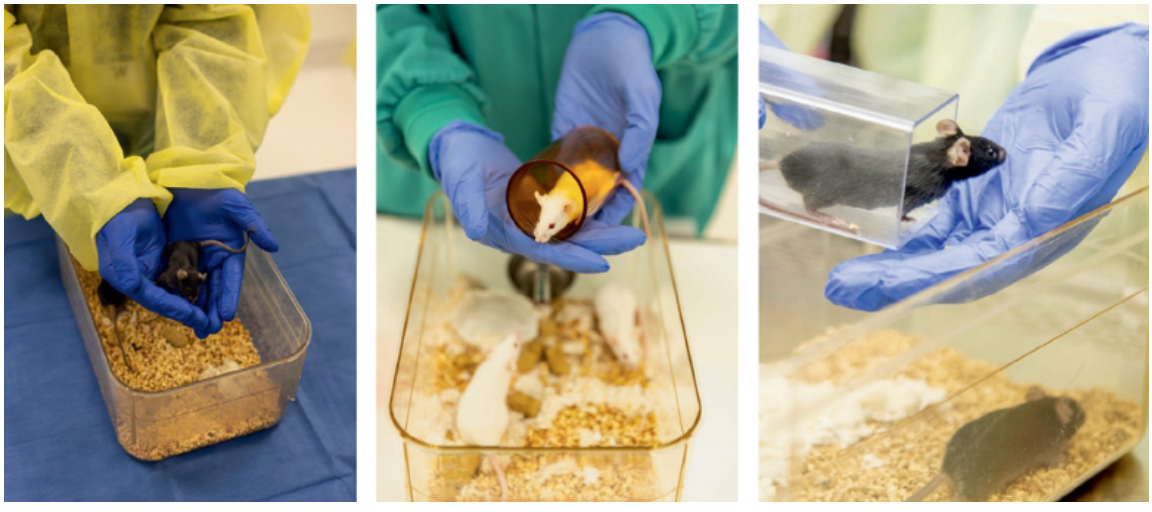
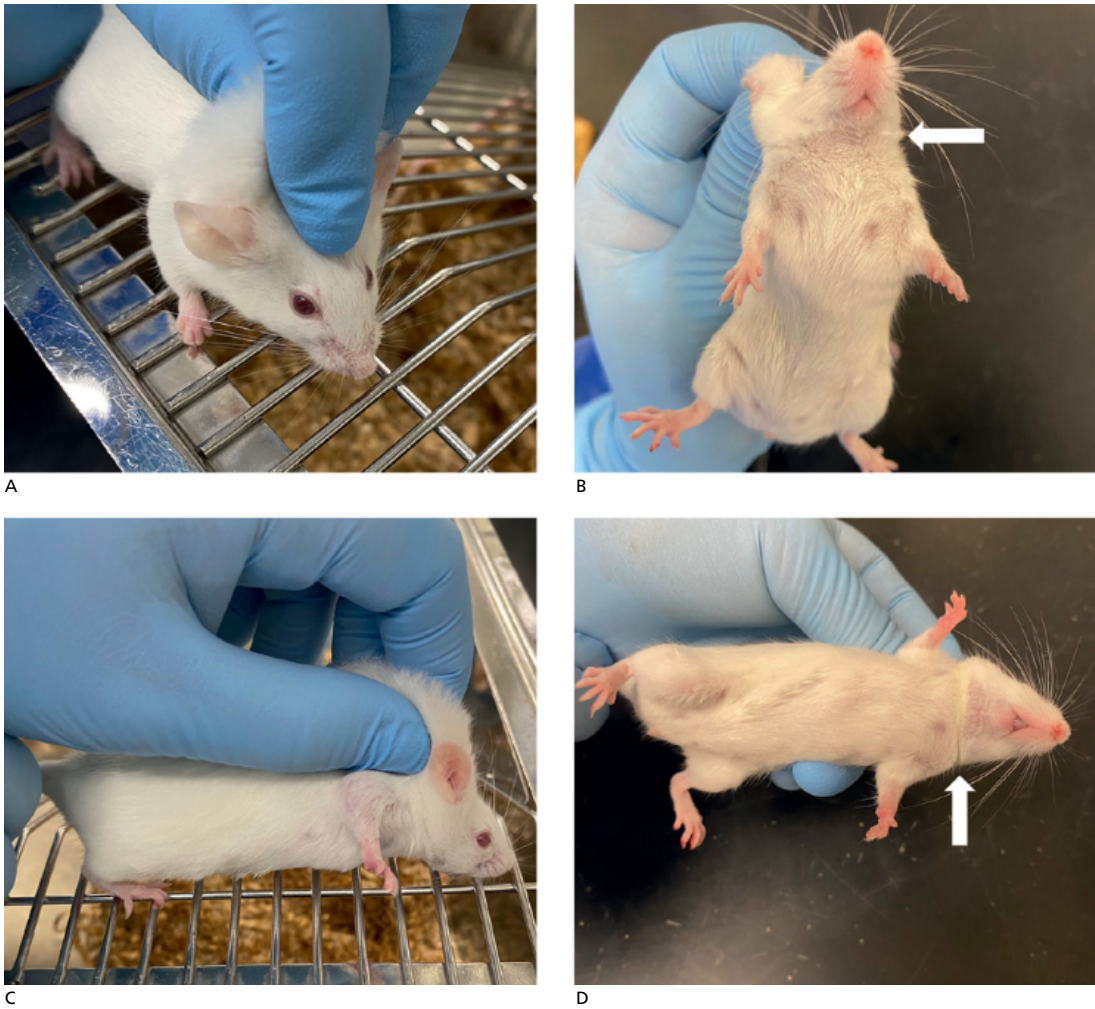


FIGURE 2.86. Low-stress handling refers to how the mouse is picked up from its home cage. Different methods can be used, including cupping the mouse with the hands (left) or using a tunnel or other piece of cage furnishing to pick up the mouse (middle and right). Once out of the cage, the mouse can be more firmly restrained for examination or treatment. Courtesy of E.A. Nunamaker.

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A B C D

FIGURE 2.87. Traditional scruffing restraint for mice can result in dyspnea and bradycardia because of a crease around the ventral neck (C & D). A 3-finger restraint technique (A&B) avoids this risk. Courtesy of R. Labitt.

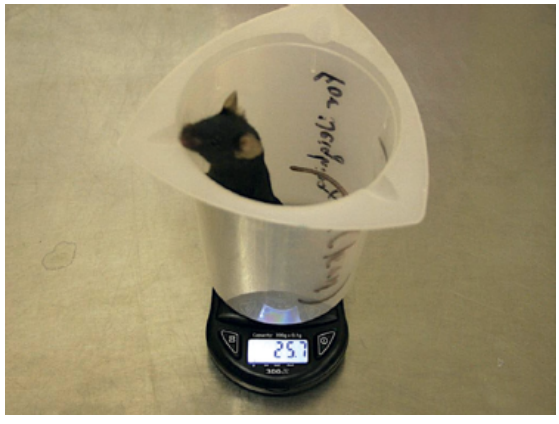


FIGURE 2.88. Small plastic containers may be used to accurately weigh mice. Courtesy of A. Martyn.



FIGURE 2.89. Large shoebox mouse cage in research setting. Complexity is provided through the use of shelters, objects to chew, social housing, and nesting material.

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FIGURE 2.90. A variety of commercial enrichment devices are available for mice and may be used to create cage complexity. There are four mice in this cage.



FIGURE 2.91. Housing for a companion mouse. The use of a shelter helps to improve feelings of security for mice. Courtesy of Calgary Avian & Exotic Pet Clinic.

ways. Owners should use caution when adding running wheels, as mice may catch their limbs between the wheel spokes if they are set too far apart and may fracture their legs.

Temperatures in mouse rooms should be maintained between 20 and 26 °C (64–79 °F), with an approximate average of 22 °C (72 °F). The ambient temperature range in which thermoregulation occurs without the need to increase metabolic heat production or activate evaporative heat loss mechanisms is known as the thermoneutral zone (TNZ), and is bounded by the lower and upper critical temperatures. The TNZ of mice is 26 and 34 °C. Laboratory mice prefer temperatures that are several degrees warmer than the environments in which they typically are housed within research facilities. Physiologic changes to rodents that are housed under standard temperatures (20–26 °C) may be associated with "cold stress" and include alterations in metabolism, cardiovascular parameters, respiration, and immunologic function. Unlike many large endotherms, mice do not have stable core temperatures. Their body temperature oscillates over short bursts of approximately 1 °C even within the TNZ. Mice will use in-cage resources, such as nesting material (Figure 2.92), substrate, and shelters, as well as behavioral modifications, such as huddling together, to adapt behaviorally to the microenvironment temperature.

The relative humidity in mouse rooms should be maintained between 30% and 70%, although this can be hard to maintain in some places during the winter and may require portable humidification to ensure that levels are adequate when external temperatures are cold and dry. Sloughing of the distal tail tip ("ringtail," see Chapter 5) may occur in neonates and weanlings when the relative humidity is excessively low. Cage filter lids or covers of any type that retard diffusion of air may increase ambient cage temperature, relative humidity, and ammonia levels, making temperature and odor control more difficult. Exposure to excessively high levels of ammonia can irritate and damage the nasal epithelium. The ILAR *Guide* recommends adequate ventilation to maintain appropriate air quality and dilute gaseous contaminants, but maximums for ammonia and carbon dioxide concentrations are not specified. Instead, a performance standard is described, setting maximal concentrations of waste gases "below levels irritating to mucous membranes." In research settings, these filter lids are placed on cages to minimize cross-contamination of pathogens among cages. Ventilated cage racks overcome the problem of increased temperature and humidity within covered cages by increasing the number of air changes per hour. The increased air flow may sometimes result in chilling of young or hairless animals and interfere with mouse communication and breeding performance. Ensuring sufficient substrate and nesting materials is particularly important with these types of caging.

Mouse caging, as for all animal caging and bedding, should be cleaned or changed as often as necessary to prevent accumulation of odor and waste and to keep the animals dry and clean. Timing of changes will depend on the cage population and type of cage system being used. Static cages may require cleaning twice weekly, whereas individually ventilated cages may only require changing once every 2 weeks.

Mice reared in colonies used for "pinkie" production for reptile or raptor feeding are often housed in large multifamily units with as many as a hundred or more animals per enclosure. These groupings can lead to significant amplification of enzootic diseases, especially if new mice are added, and if husbandry provisions are suboptimal. Smaller groupings will also help to reduce fighting within enclosures.

Feeding and Watering

Mice should be fed a clean, wholesome, and nutritious pelleted rodent diet ad libitum and watered with an automatic watering system, water bottles with sipper tubes, disposable water bottles or pouches, or water-based gel packs.

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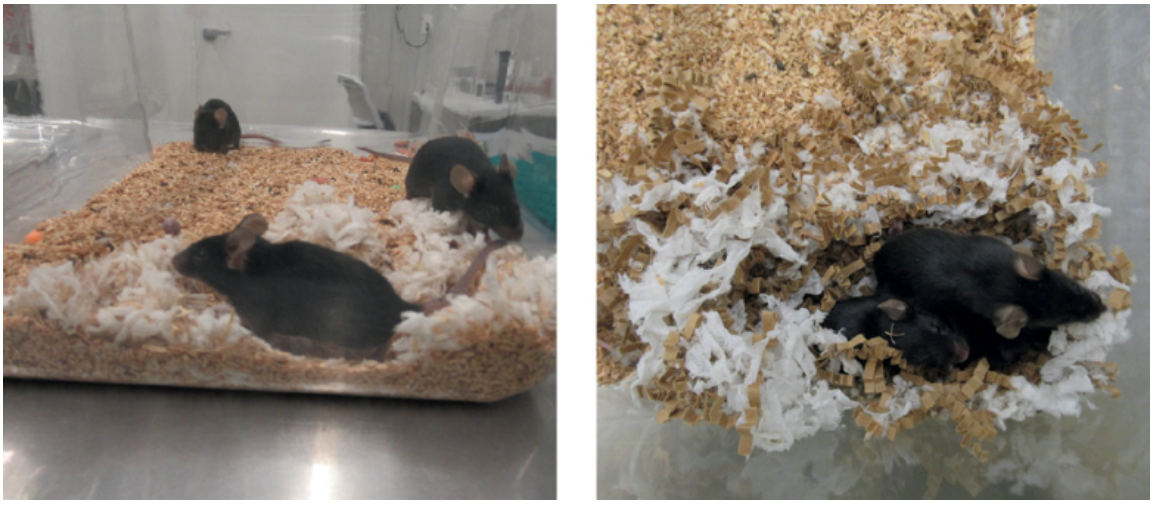


FIGURE 2.92. When given sufficient nesting materials, mice will rapidly create a nest within an hour of being introduced to a new cage. Mice continue to modify the nest, creating more complex structures over time. On the left, the image demonstrates mice starting to creating a nest within a few minutes following a cage change. On the right, within an hour, the mice have created a new nest. Small food foraging items such as seeds or other low-fat, low-calorie treats can be added to the cage substrate to encourage digging and exploration (left image).

An appropriate source of fresh water is critical, and young animals may die within 24 hours if water is not available.

Several types of special-purpose rodent diets are available, including a wide variety of pet "treats" and feeds. While mice enjoy treats, as for other pet species, to minimize the development of obesity and other health-related disorders, treats should not make up more than 5–10% of the daily diet. The most balanced diet for rodents, including rats and mice, is commercially available pelleted rodent laboratory or pet diets. Regardless of the source, to ensure high nutrient content, the food should be purchased in small quantities, stored in a dark, dry, and cool place, and used within 6 months of milling. Special diets that have been irradiated or are suitable for autoclaving can be used for immunodeficient or barrier-reared mice in laboratory settings. While most commercial rodent pellets are produced by open-formula process, closed-formula diets and those certified free of contaminants are also available for use in research colonies.

Diets for maintenance of nonbreeding adults usually contain 4–5% fat and approximately 14% protein. Diets for growth and reproduction contain 7–11% fat and 17–19% protein. Because these feeds vary in price, freshness, protein content, and quality, careful shopping and sourcing is necessary. The ideal weight for a mouse can be estimated by assessing the mouse's Body Condition Score (Figure 2.93) and adjusting food intake, if needed. Fresh water and a high-quality pelleted feed provide a complete diet; sweets, low-protein treats, supplemental vitamins, salt blocks, and vegetables are usually not necessary and may even lead to illness.

An adult mouse will consume approximately 15 g of feed and 15 mL of water per 100 g body weight per day. Water and feed consumption vary with the ambient temperature, humidity, water availability, dryness of the feed, breeding status, feed quality, and state of health.

Reproduction

Sexing

Neonatal males may be distinguished from females by a greater anogenital distance in males (1.5–2 times), the pale testes visible through the abdominal wall, and the larger genital papilla. In females, the conspicuous row of teats at 9–13 days of age is a distinguishing feature, because, as for male rats, gerbils, and rabbits, there is little development in male mice (Figures 2.94 and 2.95).

Estrous Cycle

Although female mice may have a first estrus at 28–40 days, they are generally first bred when aged 50 or more days (20–30 g). Mice bred too young or after 10 weeks have reduced fertility. The onset of sexual maturity varies with strain, season, growth rate, litter size, and level of nutrition. The estrous cycle lasts 4–5 days, with an average evening estrus period of 12 hours. Except for postpartum estrus, estrus does not occur during lactation. Group-caged female mice may enter a period of continuous anestrus, which is terminated by the odor or presence of a male. Most females will then come into sexual receptivity in approximately 72 hours, a synchronization of estrous cycles known as the Whitten effect. Pseudopregnancy may prolong the interval between estrous periods.

During proestrus the vaginal smear contains epithelial cells with some cornified cells and leukocytes; in estrus, cornified cells predominate. In late metestrus and diestrus, cornification decreases and lymphocytes increase.

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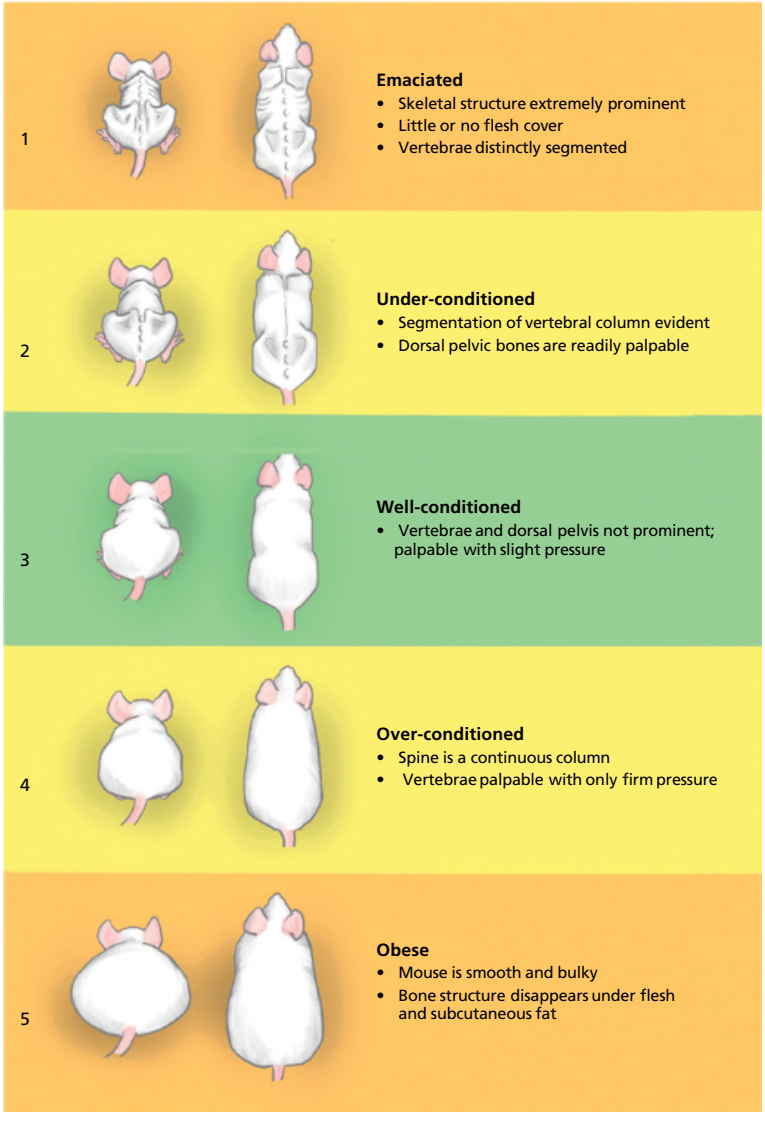


FIGURE 2.93. Body Condition Scoring for mice. It is preferable to conduct the BCS assessment by gently feeling the mouse for sharp bony prominences (a sign that the animal may be too thin) or a lack of bony structures (obese). Image by K. Sokolowski.

Breeding Programs

Considerations in mouse breeding programs include space availability, strain fecundity, inbreeding schemes, concerns about maintenance of a SPF colony, and production requirements. Mice are continuously polyestrous with minor seasonal variations. Mice have a fertile, postpartum estrus occurring 14–24 hours after parturition, which allows lactation and gestation to occur simultaneously. Therefore, many breeding schemes use the postpartum estrus for increased production. Representative breeding systems for mice include colony, monogamous, and polygamous mating schemes. In colony mating, one male and two to six females are housed together continuously, and the young are removed at weaning. This system is the most efficient of all for use of space and labor, but record keeping is difficult.

The monogamous system involves the constant pairing of one male and one female. The young are removed before the next parturition. This system, which also uses the postpartum estrus, produces the maximum number of litters per female in the shortest time and provides for ease of record keeping and evaluation of individual production. Disadvantages of monogamous breeding include the need to maintain a larger

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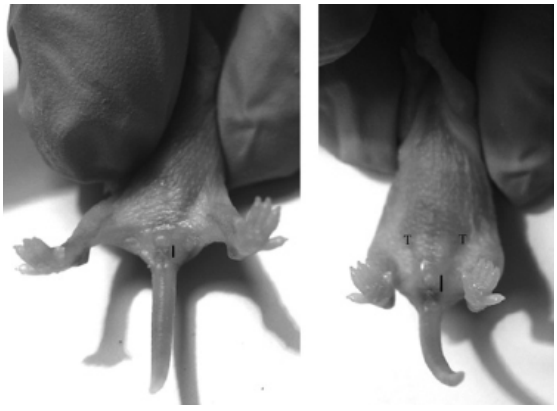


FIGURE 2.94. External genitalia of 5 day-old female (left) and male (right) mouse pups. The distance between the urogenital papilla and the anus (black bar) is longer in the male at this age. The testes can be seen through the abdominal skin of the male (T). Courtesy of Amanda Martyn.



FIGURE 2.95. External genitalia of a 10 week-old (mature) female (left) and male (right) mice. The distance between the urogenital papilla and the anus (black bar) is almost twice as long in the male, nipples are clearly seen on the ventral abdomen of the female, and scrotal sacs are present in the male. As in other female rodents, the mouse has three external openings: the urethral papilla, the vaginal opening, and the anus.

population of males and the increased need for labor, space, and equipment to service the increased populations.

A polygamous or harem scheme combines one male and two to six females. Females are removed to separate cages before parturition and the postpartum estrus is not used. In this system, each female provides more milk, larger young, and more young weaned per litter. Dams and sires are also readily identified for breeding records. Disadvantages include lower total litter numbers and increased labor time per cage.

Pregnancy and Rearing

Detection of sperm by vaginal examination or the presence of a coagulation or postcopulatory plug (a small waxy coagulum) in the vagina is evidence of mating within the past 24 hours. Note that it is not uncommon for the plug to fall out before it can be detected, and it can be difficult to see in the bedding. Checking for plugs early in the morning will increase the chance of observing them in situ. As gestation proceeds, the mammary structures develop, and the fetuses can be palpated. Daily weighing will reveal an increased rate of weight gain approximately 13 days into gestation. Mammary development is pronounced at 14 days.

In dams without current litters, the gestation period ranges from 19 to 21 days. Simultaneous lactation and pregnancy delays uterine implantation of conceptuses and prolongs the gestation period 3–10 days, depending on the size of the nursing litter. The gestation period in hybrid mice tends to be shorter than the period in inbred mice. If a mouse bred within the previous 24 hours is exposed to a strange (non-sire) male, particularly of a different strain, the implantation may be blocked. This phenomenon is called the "Bruce effect."

Pseudopregnancy in mice is noticed rarely but may follow male overuse and sterile matings. Pseudopregnancy may last 1–3 weeks. Mice routinely prepare small sleeping nests in the bedding. The hollowed brood nest, which may contain one or more families, depending on the housing and breeding scheme, is prepared in late gestation. The female spends much time with the young and usually will retrieve scattered young to the nest. In harem breeding arrangements young may suckle several lactating dams. In large-scale group housing used by noncommercial hobbyists, the young from several litters may be piled together in a nursery and managed by one of several dams sequentially.

Litter size varies considerably with strain and age. The first litter is usually smaller, with optimal production (10–12 pups) occurring between the second and eighth litters (Figure 2.96). Inbred strains usually produce smaller litters than do hybrid, outbred, or random-bred animals. Predictably, disease and nutrition status also influence productivity.

Young mice are weaned at approximately 21–28 days (10–12 g). Small mice of slower-growing inbred strains may be weaned as late as 28 days of age. In the wild, litters of mice disperse from their nest at 4–6 weeks of age. If the postpartum estrus is not used, the female resumes cycling 2–5 days postweaning.



FIGURE 2.96. Dam with nursing pups.

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Mutilation and cannibalism of the young are uncommon among mice, but whelping or recently whelped female mice should remain undisturbed for at least 2 days postpartum. These aggressive behaviors may be strain related. Mice have a highly developed sense of smell and acute hearing. High-pitched sounds (ultrasonic) may cause audiogenic seizures in some strains (e.g., DBA/2) and interfere with communication between dams and pups, leading to associated destruction of litters.

Disease Prevention

In addition to the routine husbandry precautions listed in Chapter 1, systematic diagnostic evaluation of colony animals should be conducted at regular intervals to screen for subclinical infections. Filter cage covers on static or individually ventilated cages prevent or reduce airborne transmission of microorganisms within a densely populated laboratory mouse room, although such covers may increase intracage ammonia level, humidity, and cage temperature. In laboratory settings, chlorination (10–12 ppm) or acidification (pH 2.5) of the drinking water will reduce the level of *Pseudomonas* spp. contamination, which commonly occurs in biofilms and standing water, as will regular cleaning of water bottles and flushing of rack and room water lines used for automatic watering. A 10 ppm Cl_2 solution is prepared by mixing 2 mL of 5.25% sodium hypo-chlorite solution in 10 L of water. A solution with a pH of 2.5 is prepared by mixing 10 L of water with approximately 2.6 mL of concentrated hydrochloric acid (37.5% HCl by weight). Because of variations in the pH and hardness of local water supplies, the pH of the final mixture should be monitored and titrated to a pH of 2.5. Dental caries and reduced water consumption may occur following acidification or chlorination, and colonies should be monitored closely after instituting this type of change to ensure that animals have acclimated appropriately.

Wild mice carry several diseases of clinical significance and should be excluded from areas housing pet or laboratory stock. External parasites are often found on wild mice and include the mites *Myocoptes musculinus* and *Myobia muscul.* Intestinal parasites include *Syphacia obvelata*, *Aspiculuris tetraptera*, and *Rodentolepis nana*. Commonly excluded enteric and respiratory bacterial pathogens in wild mice include *Clostridium piliforme*, *Salmonella* spp., cilia-associated respiratory (CAR) Bacillus, *Mycoplasma pulmonis*, and *Citrobacter rodentium*. Mouse hepatitis virus has been detected in a small percentage of urban wild mice and is found in virtually all pet-store mice. Pet-store mice have greater serologic prevalence of epizootic diarrhea of infant mice virus, mouse parvovirus, minute virus of mice, and mouse rotavirus than urban wild mice. Murine cytomegalovirus is found frequently in wild mice in both urban and rural environments. A similar virus was previously identified in wild mice and classified as Murine Chappaparvovirus, suggesting that these two viruses are the same, and belong to a genus that is unique from other mouse parvoviruses. This pathogen has also been called "inclusion body nephritis/nephropathy" based on its histological characteristics. MKPV has the potential to cause significant clinical disease in immunodeficient mice, including tubular degeneration, interstitial fibrosis, necrosis, and eventual renal failure, leading to death within 4–5 months.

Stress involved in shipment of mice (packing, unpacking, loading, and unloading) may cause immune function depression. A post transport stabilization period of at least 5–7 days prior to initiation of research studies using animals allows the immune system to return toward normal. Studies using reversed light cycles may require longer periods for animal acclimation. Habituating animals to handling and research techniques will extend this interval.

Public Health Concerns

Salmonellosis and lymphocytic choriomeningitis are zoonotic diseases of rare occurrence in laboratory mouse colonies. The pathogens of these diseases are more common in noncommercial settings or in pet store stock. Over 35 diseases may be transmitted by pet and wild rodents. Notable pathogens that have been detected in pet mice include *Streptobacillus moniliformis* (the agent associated with "rat-bite fever") and the tapeworm *R. nana*. Good hygiene practices, including appropriate hand washing, should always occur after handling these species. Rabies vaccinations usually are not indicated for persons bitten by companion or laboratory rodents because these animals have reduced opportunity for exposure to commonly infected animals, such as skunks, raccoons, or bats. The exception to this is wild rodents that may occasionally be adopted as pets. There is no currently approved rabies vaccine for pet rodents.

Cutaneous and respiratory allergies to rodent dander or urinary proteins commonly develop in people who own or work with mice for extended periods of time. Urinary allergens are a major source of inhaled allergenic protein for laboratory animal workers. Such allergies are not always accompanied by a positive skin reaction to injected dander, and a physician's advice should be sought if itching, reddening, runny nose, sneezing, or difficult breathing follows exposure to rodents. Allergies can become life threatening and appropriate personal protective equipment—such as dedicated lab clothing, lab coats, gloves, and face or respirator masks—is advisable to minimize exposure and personnel risk in addition to ensuring that appropriate engineering controls are in place to reduce exposure risks for personnel.

Uses in Research

It is difficult to accurately estimate the numbers of mice used annually in research in the United States because these numbers aren't formally tracked. Estimates range from at least 10 to 30 million/year. Approximately 1.3 million mice are used annually in Canada for research, education, and testing. Uses include safety testing of new therapeutics, genetics, aging, infectious disease, histocompatibility, hemolytic anemia, congenital defects, neoplasia, radiobiology, amyloidosis, autoimmune disease, congenital athymia, obesity, dwarfism, monoclonal antibody production, diabetes mellitus, renal disease, and behavior.

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Table 2.8. Biodata: mice.

Adult body weight: male	20–40 g
Adult body weight: female	18–35 g
Birth weight	0.75–2.0 g
Body surface area (cm^2)	10.5 × (weight in grams)$^{2/3}$
Rectal temperature	36.5–38.0 °C (97.7–100.4 °F)
Diploid number	40
Life span	1.5–3 yr
Food consumption	12–18 g/100 g/d
Water consumption	15 mL/100 g/d
GI transit time	8–14 hr
Breeding onset: male	50 d
Breeding onset: female	50–60 d
Estrous cycle length	4–5 d
Gestation period	19–21 d
Postpartum estrus	Fertile
Litter size	4–12
Weaning age	21–28 d
Breeding duration	7–9 mo
Commercial production	6–10 litters
Young production	8/mo
Milk composition	12.1% fat, 9.0% protein, 3.2% lactose

Biodata

The values listed in Table 2.8 are approximations only and may not represent the normal range in a given population.

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Online Resources for Mice

https://www.animalhumanesociety.org/resource/mouse-care—care of pet mice.
https://www.merckvetmanual.com/all-other-pets/mice/introduction-to-mice—care of pet mice.
https://www.thesprucepets.com/choosing-and-caring-for-pet-mice-1236741
http://www.cdc.gov/rodents/diseases/index.html—a listing of zoonotic diseases of rodents.
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https://mouse.brain-map.org/static/atlas.



THE RAT

The domesticated variety of the brown or Norway rat, usually represented by the albino or piebald animal in pet stores or research colonies, is an Old World import that occupies a long-standing and important place in biomedical and behavioral research. Rats are easily maintained and handled, inexpensive, relatively disease resistant, and suited for a range of research endeavors. They make excellent pets, being able to learn their names, come when they are called, and readily distinguish between two human caregivers.

Origin and Description

The laboratory rat, *Rattus norvegicus*, is a rodent of the family Muridae. Wild rats originated, in recent times at least, in the temperate regions of central Asia, from southern Russia through northern China, and are burrowing colonial animals. Through migration along trade and military routes, the cosmopolitan rat has spread around the world. The rat has no special connection with Norway, likely acquiring this connotation when seen centuries ago on seafaring Norwegian ships.

Domesticated rats were raised by fanciers in the seventeenth century and for combat with terriers (rat-baiting) in subsequent centuries. By the mid-nineteenth century, rats were being used in scientific experimentation. Rats, similar to mice, are available in various microbiologic (germ-free, gnotobiotic, specific pathogen free, and conventional) and genetic varieties; however, most research rats are barrier-raised in

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specific pathogen-free colonies. Commonly available stocks (outbred animals) include Sprague-Dawley and Wistar, and common strains include Long–Evans and Fischer 344 rats, although numerous other types are available. There are seven varieties, including standard, hairless, Rex, tailless, dumbo, satin, and bristle coat, and 40 distinct colors of fancy rats recognized by the American Fancy Rat and Mouse Association. These varieties, as well as crosses of common research strains, are kept as companion animals.

The Sprague-Dawley rat, an albino, has a narrow head and tail longer than the body, whereas the Wistar rat has a wide head and shorter tail. The Long–Evans and other hooded varieties are smaller than the albino strains and have darker hair (tan to black) over portions of the head and anterior body. Proportions of darker-to-white hair vary (Figure 2.97). Strain-related aggressiveness and disease susceptibilities exist among the several varieties of domestic rats, but the variation is so great that dogmatic statements would have innumerable exceptions.

Examples of outbred and mutant stocks and inbred strains of rats of biomedical interest include N : OM (Osborne–Mendel), highly susceptible to murine mycoplasmosis; SDN:SD (Sprague-Dawley), high incidence of spontaneous mammary tumors; BUF/N (Buffalo rats), thyroiditis and resistance to nephrosis; Rochester/Wistar, interstitial cell tumors; Long–Evans cinnamon, Wilson's disease; SHR/N, spontaneously hypertensive rat; Brattleboro rat, diabetes insipidus; and the Gunn rat, hepatic jaundice.

The black or roof rat, *Rattus rattus*, is seen occasionally in research colonies. This rat is smaller than *R. norvegicus* and is better adapted to tropical climates. Rats native to North America include the cotton rat, *Sigmondon* spp.; and the kangaroo rat, *Dipodomys* spp.

Anatomic and Physiologic Characteristics

Rats, similar to other laboratory murine rodents, have a baculum or os penis, a (unilateral) dental formula of 1/1 incisors and 3/3 M with continuously erupting incisors, cheeks that close into the diastema separating incisors from the oral cavity, an open inguinal canal, a divided stomach and large cecum, an articulated mandibular symphysis, both pectoral and inguinal mammary glands extending dorsally, and a diffuse pancreas. Rats have no gallbladder. They have a tapered head with pinnae relatively smaller than those of the mouse, a long often hairless tail (as long as 85% of the total body length, and proportionately longer in females than in males), and an anus usually pressed against the ground.



FIGURE 2.97. A Long–Evans rat.

The gnawing apparatus, shared with other rodents, is remarkable. The continuously erupting (hypsodontic), chisel-like incisors and powerful jaw muscles all contribute to the rat's omnivorous habits and gnawing ability (Figure 2.98). The 12 M are rooted permanently (brachiodontic), located far back in the mouth, and are used for grinding.

Rats and other rodents have masses of brown fat in various cervical locations and between the scapulae, particularly in young animals. This fat serves neonatal and cold-stressed rodents as thermogenic material for metabolic regulation. The quantity and significance of brown fat diminish into puberty and adulthood.

Albino rats have poor eyesight and depend more on facial vibrissae, hearing, and acute olfaction for sensory input. Blinded rats may appear essentially normal, although these animals may have diminished capacity to learn behaviors associated with visual cues. Behind the rat's eyeball lies a pigmented lacrimal gland called the Harderian gland, after the seventeenth-century anatomist Jakob Harder. This red-brown horseshoe-shaped gland, larger than the eyeball itself, produces lipid and red porphyrin-rich secretions that lubricate the eye and lids and may play a role in determining neonatal pineal rhythms. In some stressful situations, for example, prolonged physical restraint or lack of access to food, or in acute illnesses, the red tears may not be groomed over the pelage but instead may accumulate and stain the face, nose, and forepaws, termed chromodacryorrhea. The dried red porphyrin crust fluoresces bright red under ultraviolet light and contains no blood.

Male rats exhibit a prolonged period of growth, and ossification of the long bones is not complete until into their second year. Murine rodents, however, become sexually mature in the first several months of life. The rat genome has been sequenced, and this information, in addition to that of the mouse, has been very useful in relating genetic structure to phenotype and function (http://rgd.mcw.edu).

Rats as Companion Animals

Behavior

Despite a well-known association with plagues, garbage, and sorcery, domestic rats are readily habituated to people if handled gently and regularly, and they make excellent quiet, clean, easily trained pets that rarely bite. Rats are highly sociable, and several males and females may be combined in a single, large cage. Young are raised communally with shared nursing responsibilities. Ultrasonic (US) communications are used frequently between dams and their offspring as well as between juveniles and sexually mature adults seeking mates.

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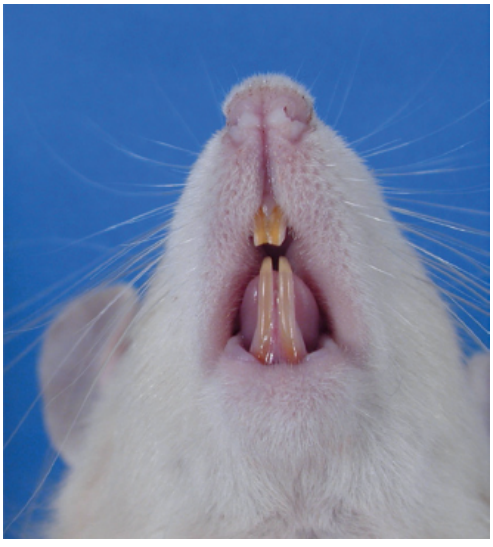


FIGURE 2.98. Normal rat incisors. Note the relative lengths of the maxillary and mandibular incisors.

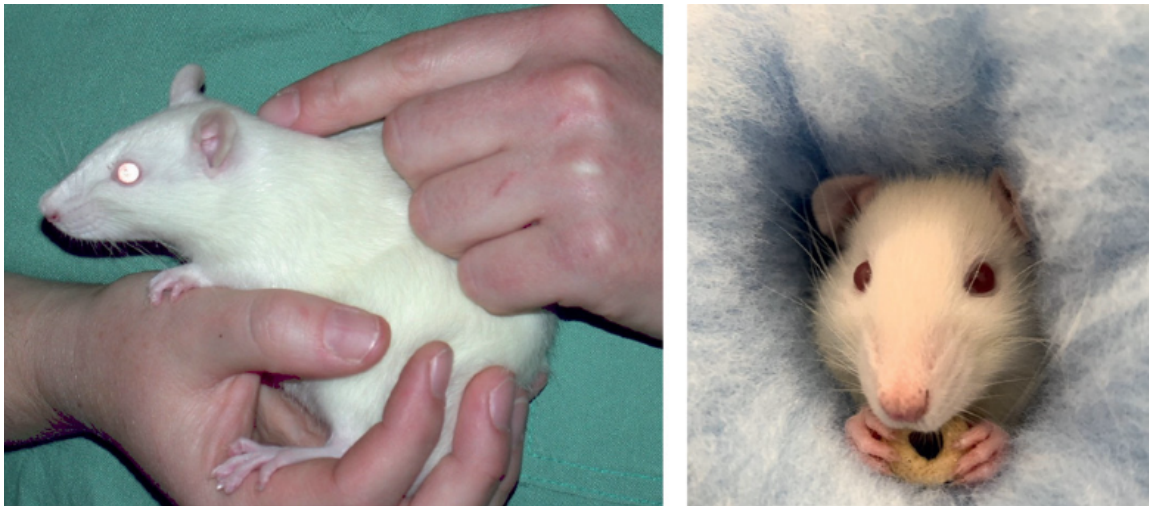
Several different ultrasonic classes of vocalization are defined for rats, including 40 kHz distress calls when pups are separated from their dams, 20 kHz calls that are made under aversive conditions, such as fighting, and 50 kHz calls that are made during play, sexual activity and other positive rat–rat social situations. As per other rodents, rats can make several audible noises that require context for interpretation. Rats can grind their teeth lightly ("bruxing") when content and can also grind their teeth more loudly ("chattering") when in pain or significant distress. The latter may be accompanied by chromodacryorrhea and a staring hair coat. Rat eyes may be seen to vibrate or bulge from their sockets slightly ("boggling") when they are bruxing. Fighting occurs rarely among sexually mature adults that have been raised in close association, although sires may bother the young, and postparturient dams may fight among themselves. Rats are gregarious burrowers, explorers, great climbers, omnivores, extensive chewers, usually nocturnal, and are year-round breeders in captivity. Escaped rats often will return to their cages.

Life Span

Rats generally live at least 24 months, although some may live longer than 3 years. They have a productive breeding life of approximately 9–12 or more months, during which time they may bear 7–10 litters with 6–14 offspring per litter. Life span is extended in some strains by caloric restriction and by feeding soy protein rather than casein. After 12 months, litter size decreases, and litter interval increases until sexual senescence at 450–500 days.

Handling and Restraint

Rats gently handled become tame and will bite rarely unless startled or hurt (Figure 2.99). Rats can be habituated to handling in as little as 15 s/d conducted three times per week for 2 weeks. Providing a small food reward after handling will strengthen the rat's positive perceptions following human interactions. Because the tail skin may deglove, the tail should be grasped only at the base and for short periods (Figure 2.100). Nonaversive or low-stress-handling methods are less well



A B

FIGURE 2.99. Gentling a rat. A. Holding newly acquired rats for at least 15 seconds several times over the course of a week will allow the animals to rapidly habituate to handling. B. Rats enjoy sitting on soft fleece. This rat has received a food treat as part of a positive human interaction experience.

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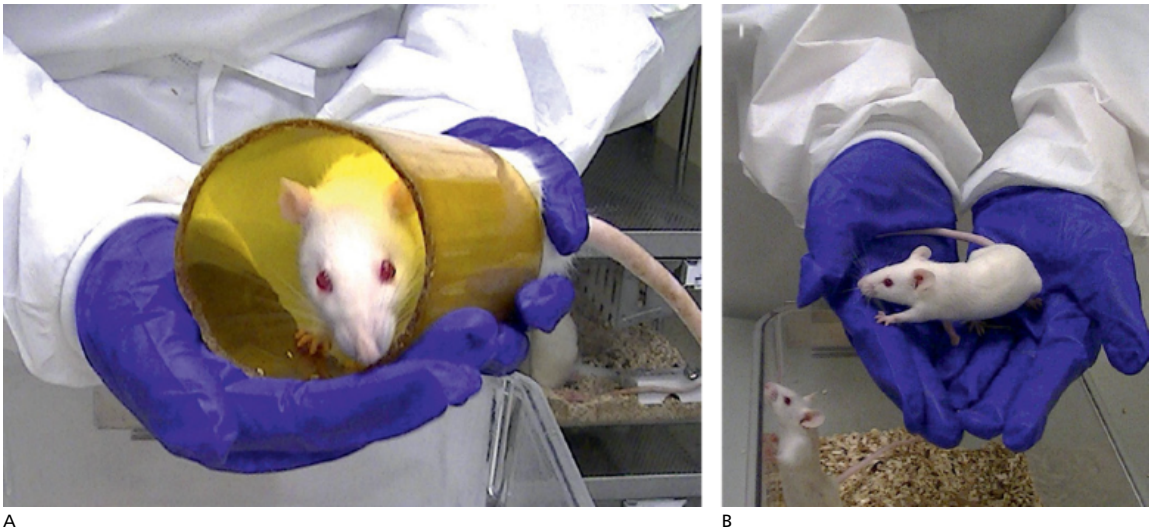


FIGURE 2.100. Tail necrosis in an animal incorrectly restrained by the tip of the tail. Treatment included tail tip amputation under anesthesia.

defined for rats. Rats may be picked up from their home enclosure with tunnels or small containers, or they may be picked up by scooping from underneath with one or both hands (Figure 2.101). When firmer restraint is needed, such as for administering treatments or during close examination, rats are picked up by placing the hand firmly over the back and rib cage and restraining the head with thumb and forefinger immediately behind the mandibles (Figure 2.102A). When longer restraint is needed for procedures, a variety of commercial restraint devices are available (Figure 2.103). Small plastic containers or tunnels may be used to remove fractious animals from their cage. Plastic containers are also useful for obtaining accurate body weights for treatments (Figure 2.102B). Rat tickling (Figure 2.104) has also been used as a positive handling technique in research settings, and was developed by neuroscientists studying play behavior in juvenile rats, including evidence of positive emotions and ultrasonic vocalizations in rats. Not all rats wish to be tickled, and it is an activity that may become less preferred with age, as animals become stiff and heavy. The technique involves gently flipping the animal on its back in the home cage and gently tickling the belly with the fingertips for a few seconds. Rats that enjoy this activity will often emit 50 kHz US vocalizations and come back to the handler for more while rats not enjoying the interaction will run away from the handler once released. Animals not enjoying the activity should not be forced to engage.

Housing

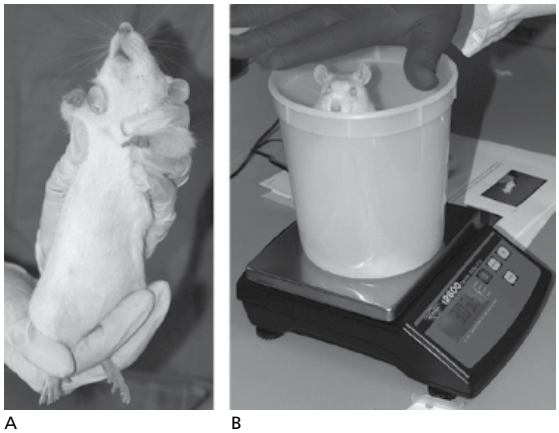
Rats are housed preferentially in plastic or wire-sided cages with solid floors (Figure 2.105). Plastic cages generally allow enhanced visibility of animals in the cage as well as improved ventilation. The plastics chosen for rodent caging



A B

FIGURE 2.101. Low-stress handling techniques for rats. A. An adult rat being removed from a cage via a tunnel. B. A juvenile rat being removed from its cage using cupped hands. Courtesy of C.I. O'Malley.

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A B

FIGURE 2.102. A. Over-the-back restraint of a rat. For larger animals, the hind end should be supported by the second hand. B. A small plastic container may be useful for obtaining accurate body weights of rats. Courtesy of A. Martyn.



FIGURE 2.103. Various commercial restraint devices available for rats include (clockwise from top left) Decapicones® (for euthanasia), plastic restrainers of varying size, and Elizabethan collars.



FIGURE 2.104. A rat being tickled. Courtesy of J. Kylie.



FIGURE 2.105. Typical shoebox cage used for laboratory rat housing, cage lid removed. To increase cage complexity, a plastic tube, shredded paper, and nylon chew toy have been added. Shoebox cages are typically kept on cage racks within an animal room.

should be resistant to chemicals and high temperatures and maintain toughness and clarity after repeated cleaning. Certain plastics, such as polycarbonate and polysulfone, may contain bisphenol A (BPA), a chemical that has been shown to be an endocrine disrupter with estrogenic activity, and thus should be avoided to due to its potential to induce various biologic and physical changes. However, multigenerational studies have shown that BPA exposure has no effect on estrous cyclicity, copulation index, fertility index, number of implantations, gestation length, litter size, pup sex ratio, pup viability, or other functional reproductive measures in rats.

Solid bottom flooring is strongly recommended for rats to improve comfort and minimize injury risks. Rats housed on wire floors longer than 6 months may develop ulcerative foot lesions that are difficult to resolve. A homemade, shoebox-shaped cage with a hardware cloth top is satisfactory for pet rats, as are plasticized wire, multi-level rodent cages available in pet stores. Glass terraria are used commonly to house pet rodents, but care must be taken to ensure accessibility to water and feed, and good ventilation as high ammonia levels may occur if the cages are not cleaned regularly. In mice and rats, *M. pulmonis* organisms multiply more rapidly in the presence of ammonia levels of 50–100 ppm, predisposing animals to respiratory disease. Young rats housed on wire floors with insufficient nesting material and substrate may become dehydrated, especially during months when ambient humidity is low. Low humidity and ambient temperatures can contribute to a condition of dehydration and vascular shunting in neonates and weanlings known as "ringtail" (Figure 2.106).

According to the eighth edition of the ILAR *Guide*, rat cages should provide at least 187.05 cm^2 (29 in^2) of floor space per adult (up to 300 g) rat housed in groups. A female with litter requires 800 cm^2 (124 in^2) of floor space. Rat cages should be at least 17.8 cm (7 in) high. The 2020 CCAC recommends a minimum of 800 cm^2 of floor space, and occupancy should be based on the minimum floor space required per

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animal. Floor area should adequately provide a comfortable resting area, including shelter, and allow for the expression of normal behaviors (including engaging in affiliative interactions and avoiding agonistic interactions, foraging, walking, running, jumping, fully stretching laterally, and playing in young rats). Additionally, the height of cages should accommodate typical postures of rats, including the ability to stretch vertically without touching the cage top. The appropriate cage height can be approximated by measuring the length of the rat from the nose to the base of the rump and adding four centimeters to account for the additional distance needed for upright stretching with partial leg extension (Figure 2.107).



FIGURE 2.106. Ringtail may occur in suckling and weanling rats and mice when the ambient temperature or relative humidity is too low. The tail tip develops dry gangrene and will slough.

Preferred bedding substrate for rats includes recycled, shredded, or pelleted cellulose products or hardwood chip or shavings, and should be hypoallergenic, dust-free, unscented, absorptive, nontoxic, and clean. Shredded cardboard without toxic dyes and some cloth materials in good condition may also be used to create comfortable nests. Soft shavings, shredded paper, and wood wool are formed more easily into nests.

Temperatures in rat rooms should be maintained between 18 and 27 °C (65–79 °F), with the optimal ambient temperature at 22 °C (72 °F), and the relative humidity should be maintained between 30% and 70%. The use of cage filter covers (or aquarium covers) raises the ambient temperature, ammonia, and humidity levels in the cage above those of the room. Light intensity is reduced within translucent or covered cages. A 12 : 12 hour dark : light cycle is used in rat-breeding colonies as continuous light will depress cycling. Rodents, especially nocturnal rodents like rats, do very well in dimly lit rooms and should not be housed in direct sunlight. Light intensities that are typical for human environments may cause retinal degeneration and cataracts in rats. Albino strains are most at risk due to their lack of melanin for protection. Both pigmented and albino rats have shown a preference of lighting less than 100 lx compared to 100–380 lx, and albino rats may seek areas with a light intensity as low as 25 lx. To effect energy conservation and to promote both good animal health and sanitation, lights in animal rooms can be controlled by a rheostat and timer, and reduced following room sanitation and animal observation.



FIGURE 2.107. Research rat housing is receiving additional attention. This figure depicts large animal cages modified for rats with tunnels and tubes on the bottom and a hanging hammock covered with fleece. In-cage resources include paper twists, pucks of shredded paper and nylon chewing toys. Inset: Modified caging with rats. A high-level sleeping platform has also been added.

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Litter or bedding should be changed as often as necessary to keep odor minimal and the rats dry and clean; one to three bedding changes per week are usually sufficient. Cages, feeders, and water bottles should be washed once or twice weekly. Rats can be litter trained, and some pet animals are allowed free access to areas of the house that have been structured to eliminate hazards and escape areas.

Cage complexity can be enhanced with nylon or hardwood chew toys (Figure 2.108), wooden or plastic tubes (Figure 2.109), structures to climb on, and the addition of multiple levels within the cage (Figure 2.110). Exercise pens are increasingly being used when rats are housed in shoebox-style caging. Rats can be placed in exercise pens during regular daily activities, such as dosing or observation (Figure 2.111), for 20–30 minutes during cage changing (Figure 2.112).

Feeding and Watering

Rats should be provided with a clean, wholesome, fresh, and nutritious pelleted rodent free-choice diet. These commercially available pelleted diets for both companion and research rodents are complete and don't require supplementation. High-sugar and -fat treats should be avoided, and dietary supplements should not consist of greater than 5–10% of the daily food intake. A few seeds or flakes of oatmeal can be sprinkled into the bedding to encourage foraging. Special feed formulations discussed for mice can also be used for rats. Feed should be kept in a cool, dark, dry place and used within 6 months of milling to ensure appropriate nutrient content. Rats should be watered from water bottles with sipper tubes or through an automatic watering system. Rats can be cautious feeders (neophobic) if not introduced to a range of foods as young animals and may avoid strange foods or consume very small quantities initially to ensure that they are safe. This is a protective mechanism for wild rats, allowing them to escape poisoning induced by gorging on potentially

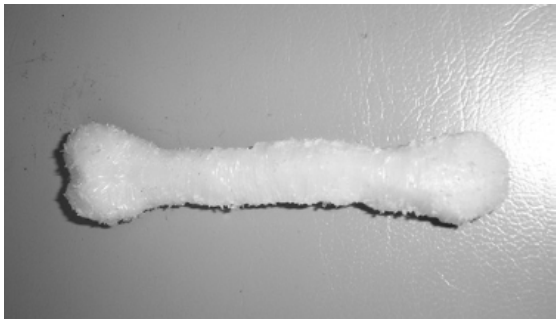


FIGURE 2.108. Nylon or wooden chew toys, such as this well-used Nylabone®, can be added to the cage for complexity. Rats may vary in their preferences for chew toys.



FIGURE 2.109. Rats will use tunnels for resting, chewing, and compartmentalizing their space. Courtesy C.I. O'Malley.

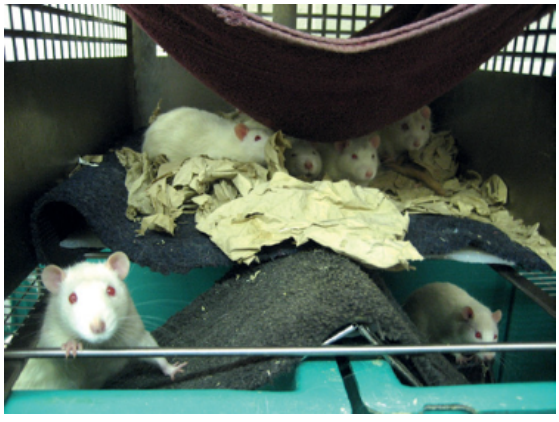


FIGURE 2.110. Colony rats housed in a multilevel rat cage with hammocks, nesting materials, and small pieces of carpet added for complexity.



FIGURE 2.111. Exercise pen for rats containing climbing objects and other novel items. This is used in conjunction with the large modified rat cage (Figure 2.107.). Animals are removed from the cage as a group and are placed into the exercise pen after dosing, weighing or other study activities. They are returned to their home cage as a group, once all animals have been treated.

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FIGURE 2.112. Exercise pen for rats used at cage change or 2–3 times/wk for rats housed in shoebox-style cages.

toxic substances. Some of the small rodent feed found in pet stores, despite attractive packaging, is inadequate in protein and energy, and it can be difficult to distinguish actual manufacturing dates. It is always recommended to buy small quantities of food at more frequent intervals than to stockpile large amounts of feed. An adult rat (300 g) will consume approximately 5 g of feed and 8–11 mL of water per 100 g body weight per day. Consumption varies with the ambient temperature, relative humidity, health status, breeding stage, diet, and time of day. Rats will display distinct dietary preferences and are attracted to odors of black pepper, milk, and coffee over those of cheese. Rats are nocturnal and feed primarily at night, consuming most of their food ration within the first few hours of the dark phase.

Reproduction

Sexing

The testicles are evident at an early age, especially if the male rat is held head up, as the testes will drop from the inguinal canal into the scrotum. Males have a larger genital papilla and greater anogenital distance than do females (5 mm in males and 2.5 mm in females at 7 days) (Figure 2.113). Female nipples are visible when the young are between 8 and 15 days old. A rapid way to sex immature murine rodents is to lift tails and compare genitalia among littermates (Figure 2.114).



FIGURE 2.113. External genitalia of an adult male rat. The paired scrotal sacs (S) are clearly visible as well as the urethral opening (U). The anus is hidden under the scrotal sacs.

Estrous Cycle

Rats reach puberty at 50–60 days, with the vagina opening at 35–90 days, and the testes descending at 20–50 days. Copulation may occur early in puberty. Strong, healthy, vigorous offspring are produced if the rats are mated first at 65–110 days of age, when the females weigh approximately 250 g and the males 300 g. The age at first mating depends on the strain and growth rate of the rat.

The rat's estrous cycle lasts 4–5 days, with an estrous period of approximately 12 hours, which, as in mice, occurs in the evening. The Whitten effect, an induction and synchronization of estrus in some females after exposure to male odor, is less pronounced in rats than in mice. Occasional induced ovulations may occur in rats.

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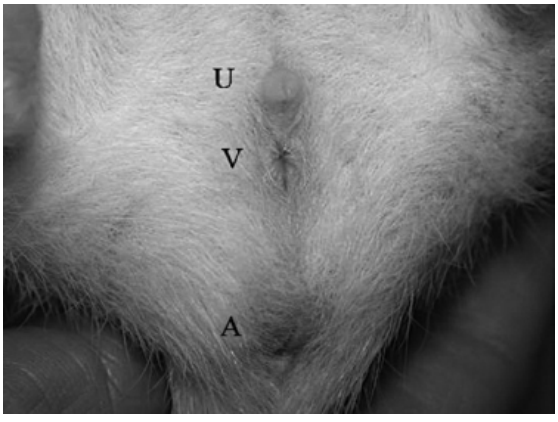


FIGURE 2.114. External genitalia of a female rat. As in the other rodent species, the anogenital distance is much shorter than in males and there are three external openings: the urethral papilla, (U) the vaginal opening (V), and the anus (A).

The short estrous cycle and the relative docility of rats allowing group housing reduce the necessity for cycle monitoring. During proestrus, the vaginal smear contains epithelial cells with some cornified cells and leukocytes, and male acceptance occurs at the end of this phase. In estrus, cornified cells become prominent, and lordosis and male acceptance occur. In late metestrus and during diestrus, cornification decreases and lymphocytes increase, and male acceptance does not occur.

Breeding Programs

Considerations in rat-breeding programs include space availability, strain fecundity, inbreeding systems, epidemiologic concerns, and production requirements. Rats are continuously polyestrous, with minor seasonal variations, and they have a fertile, postpartum estrus occurring within 48 hours of parturition. Although approximately half the females bred postpartum have live births, most rat breeders do not use the postpartum estrus because the sire may bother the neonates. The male may be removed from the cage before parturition and returned after weaning. Simultaneous lactation and pregnancy may delay implantation 3–7 days and lengthen gestation.

Representative breeding systems for rats include monogamous and polygamous systems. The monogamous system involves permanently pairing one male and one female, with the young removed at weaning or before the next delivery. This system requires a large male population and increased labor and equipment. The postpartum estrus, however, would be fertile in approximately half the rats, and, if used, would maximize the number of litters per female per unit time.

The polygamous or harem system combines one male and two to six females. Females are removed to separate cages before parturition (usually at about 16 days of gestation), and the postpartum estrus is not used. In this system, the undisturbed females provide more milk and have larger young and litters. The female is returned to the harem after the young have been weaned. If a colony system involves leaving the males and females together after delivery, removal of the young for 12 hours on the first postpartum day may facilitate postpartum mating and increase the survivability of the young.

Some commercial rat producers move the male from cage to cage; each cage contains a single female. The male remains 1 week in each cage and is reintroduced just after weaning. One male can be used for every seven females. If the male is not removed before parturition, cannibalism, litter desertion, and agalactia may result. A similar system is used for hamsters, but the females are moved through the male's cage.

Pregnancy and Rearing

After rats mate, a white, waxy copulatory plug is present in the vagina for 12–24 hours post coitum. A discharged plug may be found in the cage or litter pan. The copulatory plugs of rats tend to be dislodged more quickly than do those of mice. If mating occurs, sperm will also be present in a vaginal smear. Rats can be palpated, observed, or weighed to detect pregnancy. Mammary development is evident at 14 days.

Rats have a gestation period between 21 and 23 days, unless there is concomitant lactation, in which case gestation may be prolonged by several days. Exposure to a strange male within 24 hours of a fertile mating will not prevent implantation and luteotropic activity (Bruce effect), as may occur in mice. Pseudopregnancy is uncommon in rats, but when it occurs, it lasts approximately 13 days.

Rats build scant, shallow nests from bedding. Cotton, tissue paper, wood shavings, and shredded paper make good nesting materials. Pups born on ground corncob bedding are often exposed to the cage floor, which may cool the young and cause the dam to abandon the litter.

A few hours before delivery, the dam licks her perineum and a clear vaginal mucus appears. An average rat litter contains 6–12 young. Eyes open and hair is evident about 1 week postpartum. For the first few days after delivery, such disturbances as excessive handling, loud noises, vibration, and lack of nesting material, may cause the female rat to cannibalize her young. If the cage must be cleaned or changed, some of the nest and dirty bedding should be transferred to the new cage.

Young rats are weaned at 21 days (40–50 g). If the postpartum estrus is not used, the female rat resumes cycling 2–4 days postweaning.

Germ-free rats have been produced by hand raising under sterile conditions, and presumably rats younger than 16 days could be fed a warmed formula from a pipette.

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Young rats are chilled easily, and the food may be aspirated. Simulated maternal stimulation to induce defecation and micturition must also be provided by swabbing the perineum with a moistened cotton swab after feeding. Precautions must be taken to ensure that rodent diseases are not introduced in utero or via personnel, water, feed, cages, air, and equipment.

Disease Prevention

In addition to the usual husbandry precautions listed in Chapter 1, a systematic diagnostic evaluation of colony animals should be conducted routinely to screen for subclinical infections (i.e., a quality assurance program for monitoring animal health; see Chapter 3). Filter cage covers prevent or reduce airborne transmission of microorganisms within a densely populated rat room, although such covers also alter the cage environment. Insects and wild rodents should be excluded from rodent colonies.

Public Health Concerns

Allergies to animal dander and urinary proteins occur commonly in humans, and cutaneous and respiratory allergies to rats are very common. The urine of all rats contains a number of allergenic urine proteins (predominantly alpha$_{2u}$-globulin, also known as prealbumin), which may induce severe pulmonary and cutaneous allergies in people. Appropriate personal protective equipment such as masks, lab coats, and gloves should be considered when working with rats to minimize exposures to allergens. Large, crowded rat populations, poor air circulation, and infrequent cage changing and cleaning that lead to accumulation of ammonia gas compound the allergy problem in humans. Engineering controls, such as appropriate room ventilation and air balancing, and housing animals in ventilated cabinets, should be used to protect personnel from allergy risks.

Zoonotic diseases carried or transmitted by rats include leptospirosis, streptococcal infections, salmonellosis, cestodiasis, hemorrhagic fever with renal syndrome caused by hantaviruses, and rat bite or Haverhill fevers. Sylvatic plague (*Yersinia pestis*) is carried by rat fleas. The tropical rat mite, *Ornithonyssus bacoti*, may transmit Coxsackie virus, western equine encephalitis virus, St. Louis Encephalitis virus, *Rickettsia typhi*, *Rickettsia akari*, and *Francisella tularensis*. Both *O. bacoti* and *Laelaps echidninus* will bite humans, but rat bite dermatitis from *O. bacoti* is more commonly reported. Rat bite fever is caused by *S. moniliformis* (streptobacillosis), which can be carried in the nasopharynx of asymptomatic rats. *Spirillum minus,* another cause of rat bite fever (spirillary sodoku), is more common in Asia than in North America. People who are experiencing streptobacillosis may develop recurrent fever with petechial hemorrhages, endocarditis, and polyarthritis. Spirillary sodoku and streptobacillosis are clinically differentiated on the basis of multiple features, including a shorter onset for streptobacillosis (within 10 days) versus sodoku (14 days). Although these diseases and infections may occur in wild rats brought into a laboratory, they are rare in domestic rats, as is rabies. Excellent hygiene, including hand washing and not eating or drinking around the animals, should always be encouraged among clients, staff, and other personnel handling rats, to minimize exposure risks.

Uses in Research

Formal tracking of rat numbers used in research does not occur in the United States; however, it was estimated that there were 111.5 million rats and mice in research between 2017 and 2018. In Canada, the CCAC reports annual research rat use at approximately 130,000/year. Uses of laboratory rats include studies of aging, neoplasia, drug effects and toxicity, gnotobiology, dental caries, lipid metabolism, nutrition, behavior, alcoholism and cirrhosis, arthritis, metabolism, jaundice, hypertension, embryology, teratology, diabetes insipidus, genetics, and infectious disease.

Biodata

The values listed in Table 2.9 are approximations only and may not represent the normal range in a given population.

Table 2.9. Biodata: rats.

Adult body weight: male	300–500 g
Adult body weight: female	250–300 g
Birth weight	5–6 g
Body surface area (cm^2)	10.5 × (weight in grams)$^{2/3}$
Body temperature	35.9–37.5 °C (96.6–99.5 °F)
Diploid number	42
Life span	2.5–3 yr
Food consumption	5 g/100 g body weight/day
Water consumption	8–11 mL/100 g body weight/day
GI transit time	12–24 hr
Breeding onset: male	65–110 d
Breeding onset: female	65–110 d
Estrous cycle length	4–5 d
Gestation period	21–23 d
Postpartum estrus	Fertile
Litter size	8–14
Weaning age	21 d
Breeding duration	350–440 d
Commercial	7–10 litters
Young production	4–5/mo
Milk composition	13.0% fat, 9.7% protein, 3.2% lactose

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Chapter 3

Clinical Procedures

Clinical procedures used to diagnose and treat diseases in rabbits and rodents include sample collection for clinical and diagnostic pathology, medical imaging, ophthalmology, administration of drugs, anesthesia, analgesia, dentistry, surgery, serologic techniques, other special techniques, and euthanasia. Common diseases and their specific treatments are discussed in Chapter 5. Treatments for rabbits and rodents are often based on both species-specific information and extrapolation from other domestic mammals. However, when extrapolating from other animals note that some diseases and their treatments are unique to rabbits and rodents. In addition, marked anatomic and physiologic differences must be taken into consideration, especially regarding the teeth, the gastrointestinal system, and the ears. In some cases, treatment with drugs and regimens efficacious in larger animals may be ineffective or even harmful in small mammals. Regardless, a wealth of knowledge is currently available in rabbit and rodent medicine from various exotic pet journals and websites, as well as both the zoologic and laboratory animal medicine disciplines. When clinical information is anecdotal, the clinician should use his/her best judgment in devising a diagnostic and treatment plan that takes into consideration practical aspects as well as potential implications for ongoing research projects.

SAMPLE COLLECTION

Sample collection is a cornerstone of both research and clinical practice. Many diagnostic tests available for other animals are also applicable to companion rabbits and rodents. Limitations exist in the amount of sample that may be collected and the size of the collection devices; however, many of these limitations have been overcome with the availability of micro-collection tubes and devices and development of micro-analytical techniques. There are a number of online laboratory animal medicine resources that may be useful for demonstrating more contemporary handling, restraint, and various techniques for rabbits and rodents, such as the 3Rs Collaborative (3RsC; https://www.na3rsc.org), Research Animal Training (https://www.researchanimaltraining.com/), the RI.SE Handle With Care videos (https://www.ri.se/en/what-we-do/expertises/3r-focus-on-animal-welfare), the Norwegian Consensus Platform for Alternatives (NORECOPA; norecopa.no), and the UK's National Centre for the 3Rs (www.nc3rs.org.uk/resource-hubs). These alternative techniques encourage positive reinforcement training and voluntary cooperation of animals with procedures, which require additional time and which need to be taken into account when planning study timing. If using plastic restraint devices it is important to ensure that the animal is not squeezed too tightly and can breathe without difficulty. In research settings, rabbits or rodents that require procedural restraint for >15 minutes should be gradually habituated to the restraint device before first use (Figure 3.1). Clear plastic envelopes (e.g., DecapiCones™) should not be used for nonterminal restraint for sample collection or infusions in mice and rats, as they may overheat, have difficulty breathing, and may become excessively soiled with urine and feces. Retroorbital bleeding with recovery has largely been phased out as a blood collection technique in rodents. Both retroorbital bleeding and cardiac puncture should be considered terminal events and only performed under anesthesia followed by immediate euthanasia.

Rabbits and rodents are prey species and become stressed by activities such as transport, separation from cagemates, predator odors (e.g., dog, cat, ferret), and handling and restraint. Many prey species, such as the rabbit, will exhibit a sympathetic or "fight or flight" response, which is a display of anxiety, fear, or panic when an unfamiliar person (e.g., veterinarian or technician) or animal approaches, causing them to freeze or bolt unexpectedly. It is important to be aware of these tendencies to avoid injury to the animal and the handler during sample collection. Sedation or anesthesia should be used in stabilized animals, when needed.

Blood Collection

Collection of blood is a very common procedure conducted in laboratory animals and in small mammal companion animals, but rarely in meat rabbits. Without regular practice, samples can be challenging to obtain, especially in small rodents. However, clinically useful information can be gleaned from a

Harkness and Wagner's: Biology and Medicine of Rabbits and Rodents, Sixth Edition. Patricia V. Turner, Colette L. Wheler, Hugues Beaufrère, Niora Fabian, and John E. Harkness.
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FIGURE 3.1. Habituation of rats to inhalant nose cones in their home cage. Rats are exposed to restraint device and can choose to freely enter the restraint cones, which contain a drop of sweetened water. This helps to reduce fear when this restraint is later used on study. Courtesy of W. Archibald.

microhematocrit (MHC) (capillary) tube of blood and a well-prepared blood smear, including hematocrit, total protein, blood urea nitrogen (BUN), glucose, white blood cell (WBC) count, and a differential count. Some in-house analyzers and diagnostic laboratories can run a complete blood count (CBC), hematocrit, and several plasma chemistries with as little as 50 uL (0.05 mL) of whole blood, making this level of diagnostic medicine available to very small patients. Appropriate firm but gentle restraint, proper selection of needle or lancet size, minimizing force when transferring blood from a syringe into a sample tube, and immediately separating blood cells from plasma or serum, when indicated, will reduce artifact caused by hemolysis and increase sample quality.

Refinement of blood collection procedures used for laboratory rodents and greater expectations from companion animal owners for delivery of quality medicine to all species have motivated practitioners to become more proficient at safely collecting samples from small mammal pets. The choice of procedure depends on the species, volume of blood required, intended frequency of bleeding, whether or not anesthesia can be used, and whether the animal is a companion animal or a laboratory subject. The smallest needle size possible should be used for blood collection to reduce pain and discomfort for the patient. Whenever repeated sampling will occur over a short interval a catheter should be placed. Animals that are stressed will experience peripheral vasoconstriction making it very difficult to collect a blood sample. For research animals, habituation and desensitization to people and handling are strongly recommended to minimize animal stress during procedures such as blood collection. Small rodents and rabbits in distress (e.g., urinating, defecating, vocalizing) should be rested, and the procedure not attempted until they have become calm. Similarly, if an adequate blood sample is not obtained after a maximum of 2–3 attempts then the animal should be returned to its cage and rested before further attempts are made.

In general, peripheral sites are preferred for blood collection for all conditions and species to minimize stress from restraint, pain from venipuncture, and the risk of inadvertent exsanguination from inadequate hemostasis. Ethylenediaminetetraacetic acid (EDTA) is the preferred anticoagulant for hematology assays since it causes minimal changes to cell morphology and staining characteristics. However, it is still preferable to make blood smears with whole fresh blood before it is mixed with anticoagulant, if possible. Note that to collect a given volume of plasma or serum approximately 2.5–3 times as much whole blood is needed.

The blood volume of rabbits and rodents is ~6–8% of body weight, and approximately 10% of that can be removed at one time. A good general rule of thumb applicable to all species is that 6 mL of blood can be safely removed per kg body weight for a single sample volume. No more than 15% should be taken during a single blood draw or during a 2-week period to avoid hypovolemic shock. While blood volume is restored in 24 hours, red blood cells (RBCs) and reticulocytes take up to 2 weeks to return to normal levels; thus, the recovery period after a maximum blood draw is at least 2 weeks. Replacement of blood with fluids such as lactated Ringer's solution should be considered, especially if >10% of blood volume is taken at one time. With 20–25% acute blood loss, arterial blood pressure, cardiac output, and oxygen delivery to vital organs decreases, leading to hypovolemia and shock. Table 3.1 gives approximate blood volumes and lists suggested blood sample sizes for rabbits and rodents. For terminal blood draws, as much blood as is needed can be removed, but animals should be anesthetized or euthanatized before blood collection begins. Up to 50% of the total blood volume can be accessed as a terminal sample.

Total blood volume estimations only apply to healthy adult animals with good nutritional status, and normal body condition and hydration. For older or obese animals, maximum blood collections should be reduced by at least 15%. Pregnant or lactating animals also may not tolerate maximum blood draws.

Table 3.1. Approximate adult total blood volumes (TBV) and exsanguination volumes for rabbits and rodents.

Species	Adult Total Blood Volume (mL/kg)	Exsanguination Volume (mL)
Rabbit	44–70	60–160
Guinea pig	64–90	15–30
Chinchilla	55–70	10–18
Hamster	64–80	3–5
Gerbil	59–85	2–4
Mouse	62–80	1–1.5
Rat	58–70	8–12

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Rabbits

Common sites for blood collection in rabbits, along with recommended equipment, are listed in Table 3.2. Many rabbits can be manually restrained for blood collection, especially if it is done in a quiet, stress-free environment by competent handlers. Wrapping the rabbit in a towel facilitates restraint (see Figure 2.11 in Chapter 2 for example). Several variations of the towel-wrap have been described, but the goal of each is to prevent the rabbit from backing out of the towel and to minimize the rabbit's ability to kick and injure itself or the handler. A cat bag may be useful for larger rabbits. Commercially available rabbit restraint jackets, such as the Bunny Snuggle® (Lomir Biomedical, Inc.), are also available. Sedation may be necessary for stressed rabbits. See Table 3.13 for possible drugs and dosages.

With gentle aspiration, the marginal ear vein can be used to collect small amounts of blood. Gently rubbing or warming the ear will improve the blood flow. The vessel can be occluded by pinching or applying an elastic band or paper clip to the base of the ear. It is imperative to remove any tourniquet device when bleeding is complete to ensure adequate hemostasis. In rabbits with large ears, e.g., New Zealand white rabbits, a 25 gauge butterfly catheter can be inserted into the vein (see Figure 3.40 for image sequence of catheterization of the marginal ear vein). Thrombosis of the ear vein and subsequent sloughing of ear tissue has been reported after blood collection or catheter placement, especially in breeds with small ears; however, this is rare. Larger amounts of blood can be collected from the central ear artery either with a syringe and needle, by inserting a catheter (see Figure 3.37 for image sequence of catheterization of the central ear artery) or by allowing blood to flow freely into a collection tube directly from a needle. If necessary, a drop or two of oil of wintergreen

Table 3.2. Common sites and suggested equipment for use in blood collection in rabbits.

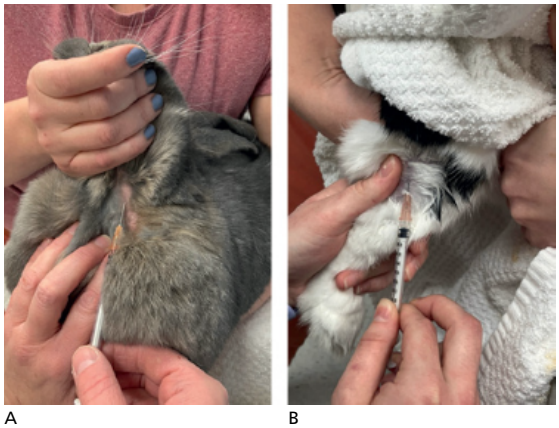
Site	Recommended Equipment		Comments
	Needle	Syringe	
Marginal ear vein	28–25 g	0.5–1 mL	Use of topical anesthetic (e.g., EMLA) facilitates collection For <1 mL of blood Place catheter for repeated blood collection Dilate with gentle warming
Central ear artery	25–20 g	3–5 mL	Use of topical anesthetic (e.g., EMLA) facilitates collection For large amounts of blood Place catheter for repeated blood collection Oil of wintergreen dilates vessel Ear hematoma if insufficient hemostasis
Cephalic vein	27–25 g	1 mL	For <1 mL of blood
Jugular vein	25–22 g	3–10 mL	For large amounts of blood Firm restraint in either dorsal or ventral recumbency (former is facilitated by anesthesia) Avoid overextending neck Approach either cranial to caudal or caudal to cranial Iatrogenic exsanguination may occur with inadequate hemostasis or if animal struggles and vessel is lacerated Less preferred site
Lateral saphenous vein	25–22 g	3 mL	For moderate amounts of blood Requires competent handler May require careful clipping of fur Vessel collapses easily Preferred site for companion rabbits
Cardiac puncture	22–20 g; 2.5–3 cm (1–1.5″)	5–35 mL	For large amounts of blood Terminal procedure Anesthesia required Can also use vacuum blood collection sets and tubes

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(also found in some rubbing alcohols) can be applied to the skin over the artery to facilitate dilation. A topical anesthetic such as a pea-sized amount of EMLA® or Maxilene® cream applied over the vessel with a cotton tipped applicator at least 10 minutes prior to arterial puncture will minimize pain and avoidance behavior, such as head jerking at the moment of skin puncture. If necessary, midazolam at 0.5–2 mg/kg IM, acepromazine at 1–5 mg/kg IM, or Hypnorm® at 0.2–0.5 mL/kg IM will facilitate restraint, vasodilation (acepromazine), and relaxation. Additional drugs and dosages are listed in Table 3.13.

The external jugular vein also can be used for collection of blood volumes greater than 1 mL, but is less preferred because there is a risk of inadvertently hitting the carotid artery and satisfactory hemostasis can sometimes be difficult to achieve. Sternal restraint, with the head extended and front legs pulled downward over the edge of the table (Figure 3.2A), similar to restraint for jugular bleeds in cats, and a lateral or dorsal restraint position, with front legs pulled caudally, have all been described. Care must be taken not to overextend the neck, or acute respiratory distress may occur. The vein is occluded at the thoracic inlet and entered from either a cranial to caudal or caudal to cranial direction, depending on the ease of access. In does, the dewlap may need to be pushed laterally or ventrally prior to venipuncture.

The "football" hold (see Figure 2.9) is useful for accessing the lateral saphenous vein. The rabbit's head can be tucked under one elbow to reduce visual stimulation while the hindleg is extended and presented to the bleeder. The vein runs diagonally across the mid-tibia and is occluded by encircling the stifle (Figure 3.2B). More than 1 mL of blood can be collected with gentle aspiration. Pressure must be applied after needle withdrawal to prevent hematoma formation. The cephalic vein can yield a small amount of blood, and restraint is similar to that for dogs and cats. The vessel can be occluded by encircling the elbow with a thumb and finger, or by using a tourniquet. Covering the rabbit's eyes with a towel may help reduce stress.



A B

FIGURE 3.2. A: Collection of blood from the jugular vein of the rabbit. To restrain the rabbit for this procedure, the rabbit's head is extended and the front legs are held over the edge of the table. B: Collection of blood from the saphenous vein of a rabbit. The vein runs diagonally across the mid-tibia. The rabbit is best restrained in the arms for this procedure. Courtesy of Calgary Avian & Exotic Pet Clinic.

Cardiac puncture requires deep anesthesia or prior euthanasia (i.e., collect immediately after the procedure) and is used for terminal blood collection in research animals or meat rabbits. In New Zealand white rabbits, an 18–21 gauge 3.75 cm (1½ in) needle attached to an appropriately sized syringe is inserted laterally through the left chest wall or from the cranial or caudal end of the sternum. Alternatively, if large amounts of blood are required, vacuum blood collection sets and tubes may facilitate collection.

For all bleeding sites, to increase visibility and facilitate collection, alcohol may be used sparingly to wet the fur over the vein, and careful clipping or plucking of hair from the venipuncture site may be necessary. Rabbit blood clots quickly, and it should be mixed with an anticoagulant immediately. To help prevent clotting, sterile heparin or sodium EDTA can be aspirated through the needle, into the syringe, and then expelled, leaving a residual amount in the needle hub. Several air-dried blood smears made with fresh blood at the time of venipuncture will prevent cell morphology changes caused by the anticoagulant in the tube during transport to a laboratory. In addition, minimizing force when transferring blood into a collection tube, removing the needle from the syringe and the rubber stopper from vacuum-sealed collection tubes before expelling the blood, and immediately separating blood cells from plasma or serum will help minimize artifact caused by hemolysis. Firm clot formation takes 30–45 minutes in rabbits. Automated flow cytometry is reliable for analyzing most hematological parameters in rabbits.

Rodents

Common sites for blood collection in rodents, along with recommended equipment, are listed in Table 3.3. A variety of commercially available and homemade restraint devices can be used for blood collection in laboratory rodents, including acrylic tubes, cloth drapes or towels, and Rodent Snuggles® (Lomir Biomedical, Inc.), which can be adapted to clinical practice. Isoflurane anesthesia is generally safe, and may be required in highly stressed individuals or to access some sites, such as the gingival sinus. Depending on the size of the rodent, blood may be aspirated directly into a syringe or collected from the hub of a needle with a MHC tube. The filling volume of the MHC tube should be noted to avoid removing too much blood, especially from mice and other very small rodents. Most tubes have a volume of ~70 µL (maximum 3–4 full tubes per mouse); however, the capacity can range from 50 µL to 100 µL or more, depending on the manufacturer. Tuberculin syringes (0.5 or 1.0 mL)

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Table 3.3. Common sites and suggested equipment for blood collection in rodents.

	Recommended Equipment	
Site/Species	Needle and Syringe	Comments
Lateral saphenous vein: Guinea pig Chinchilla Hamster Gerbil Rat Mouse	28 g attached, 0.5 mL insulin 25–20 g, no syringe 22–18 g or Goldenrod animal lancet	Direct aspiration possible in larger guinea pigs and chinchillas Place needle and collect directly from hub with MHC tube Clip fur and apply thin coat of petroleum jelly; prick vein and use MHC tube or allow blood to drip into container
Femoral vein: Guinea pig Chinchilla Hamster Gerbil Rat Mouse	22–27 g 26 g × 3/8″[a], 1–3 mL syringe	Located medially Anesthesia usually required Can place needle and collect from hub with MHC tubes in small rodents
Cephalic vein: Guinea pig Chinchilla	25 g, no syringe	Collect blood from needle hub as above
Jugular vein: Guinea pig Chinchilla Hamster Gerbil Rat Mouse	22–28 g, 1–3 mL syringe	Can attempt in the awake guinea pig, chinchilla, and rat Anesthesia required for other rodents
Cranial vena cava: Guinea pig Chinchilla Hamster Rat	22–25 g; 1.6–2.5 cm, 3–5 mL syringe	Anesthesia required Risk of death from bleeding into thoracic cavity Needle inserted at a 60° angle in a caudo-medial direction in the notch between the manubrium and the first rib.
Tail vein/artery: Chinchilla Gerbil Rat Mouse	25–28 g, 0.5–1 mL syringe	Warm tail to vasodilate vessels Can place needle and collect from hub with MHC tubes in small rodents Poke tail vein with small g needle and allow blood to drip into container
Lateral tarsal vein: Hamster	25–27 g, no syringe	Collect blood from needle hub as above
Facial vein: Mouse	8 g, no syringe or 4–5 mm Goldenrod lancet	Allow blood to drip into container – count drops and collect no more than 4–6 http://www.medipoint.com/html/for_use_on_mice.html
Gingival sinus: Guinea pig Chinchilla Hamster Rat	25–28 g, 0.5–3 mL syringe	Under anesthesia in dorsal recumbency Inferior lip pulled caudally Needle inserted 2–4 mm deep at the base of the lower incisors at a 30–60° angle (see Figure 3.4B) Not appropriate for blood culture
Submental vein: Mouse	4–5 mm lancet, up to 0.15 mL	Conscious collection, less traumatic than facial vein, count drops, and collect no more than 4–6
Cardiac puncture: All	Varies	Anesthesia required, terminal procedure

[a] Available with 1 mL syringes in BD Allergy Trays (BD-305539) (25 per tray × 4 = 100 total).

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are useful to prevent collapse of small veins when direct aspiration is performed. Some veins (tail, facial, submental, lateral saphenous) may also be punctured with a needle or lancet and blood collected directly with a MHC tube or allowed to drip freely into a tube. In mice and other small rodents, only the number of drops that make up the recommended sample volume should be collected to avoid excessive blood loss (1 drop = ~50 µL; maximum 4–6 drops in most mice). In addition, care should be taken to ensure all drops fall into the collection tube and that bleeding stops quickly to avoid wasted drops and hypovolemia. Replacement of blood with subcutaneous fluids (sterile 0.9% saline or lactated Ringer's solution), and observation in a warm (not hot) stress-free environment should be considered if excessive blood loss has occurred. Provision of a commercial gel supplement, such as DietGel® (https://www.clearh2o.com) or Electro-Gel® (https://www.bio-serv.com), on the cage floor is also helpful. An easy homemade gel supplement can also be made with unflavored gelatin and an oral nutritional supplement such as Ensure® or Boost®. A variety of different sized lancets specifically for use in laboratory animals, as well as helpful information on how best to use them, is available from MEDIpoint, Inc. (Goldenrod Animal Lancet®, http://www.medipoint.com/html/animal_lancets.html). Microcollection tubes such as Microtainer® (Becton, Dickinson & Co) or Microvette® (Sarstedt) are readily available. For tests that can be run on either serum or plasma, the yield of plasma is higher than serum for a given sample (i.e., 0.4 mL blood yields 0.2 mL plasma and 0.15 mL serum). Collection tubes with gel separators improve the plasma or serum volume recovery.

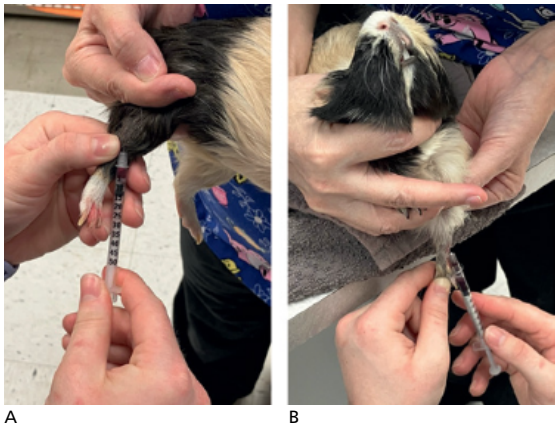
Guinea Pigs

Guinea pigs become distressed when restrained in lateral or dorsal recumbency, and they prefer to be held upright and close to the restrainer's body, or cupped reassuringly on an exam table. Their short legs and neck make it difficult to access peripheral veins without anesthesia. Small amounts of blood can be collected from the lateral saphenous vein by cradling the animal and presenting the leg to the bleeder while occluding the vein by encircling the limb (Figure 3.3A). After clipping the fur and applying petroleum jelly to the site, a 20 gauge needle or appropriately sized lancet is used to quickly and deftly puncture the vessel. The blood is collected into MHC tubes or into a container as it beads off the petroleum jelly. In very large guinea pigs and some chinchillas, direct aspiration may be successful with a 0.5 or 1.0 mL insulin syringe, using gentle suction.

The femoral vein may be used to collect up to 3 mL of blood in anesthetized guinea pigs. The animal is placed in dorsal recumbency, and the hind leg positioned with the femur at a 90° angle to the long axis of the body. The needle is inserted midway along the upper thigh at a 45° angle to the length of the femur, applying slight suction. Aspiration of bright red indicates puncture of the femoral artery, and direct pressure must be applied to the site for 2–3 minutes for hemostasis.

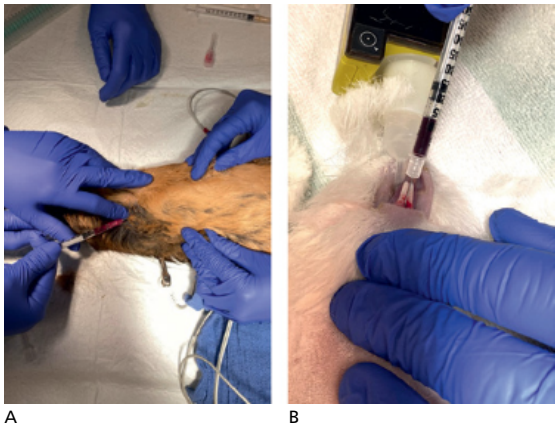
Jugular venipuncture can be attempted in unanesthetized animals using sternal restraint with the head and neck extended upward and forward to avoid respiratory distress. The vein is usually not visible or palpable, and the skin is relatively thick in this area; clipping the fur may assist in finding the vessel. If anesthesia is used, the guinea pig is positioned in dorsal recumbency, and a length of gauze looped around the upper incisors used to extend the neck. The vein is then accessed in a cranial to caudal direction.

The cranial vena cava may be used to collect large amounts of blood (Figure 3.4A); however, this technique carries with it the risk of death from bleeding into the thoracic cavity. The sedated or anesthetized guinea pig is restrained in dorsal recumbency, with the front legs pulled caudally and apart. The notch between the junction of the first rib and the manubrium



A B

FIGURE 3.3. A: Blood collection from the lateral saphenous vein of a guinea pig. B: Use of the cephalic vein for blood collection in a mature guinea pig. Courtesy of the Calgary Avian & Exotic Pet Clinic.



A B

FIGURE 3.4. A: Cranial vena cava approach for blood collection from an anesthetized guinea pig. B: Gingival blood collection from an anesthetized guinea pig.

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is palpated, and the needle inserted at a 60° angle to the body, aimed toward the midline right under the manubrium. The vein is usually fairly superficial. Slight suction is applied as the needle is advanced. Alternatively, for terminal bleeding, blood may be collected by cardiac puncture under deep anesthesia using either a left lateral or ventral midline approach.

Collection of blood from the cephalic vein can be difficult due to the guinea pig's short forearm. It may be possible to use a MHC tube to collect blood directly from the hub of a needle placed in the vein (Figure 3.3B). Toenail clipping is very painful, is not permitted in many jurisdictions in research guinea pigs, and should not be used as a means of blood collection. In laboratory animals, implantable catheters for multiple blood sampling can be placed in the carotid, jugular, and femoral veins.

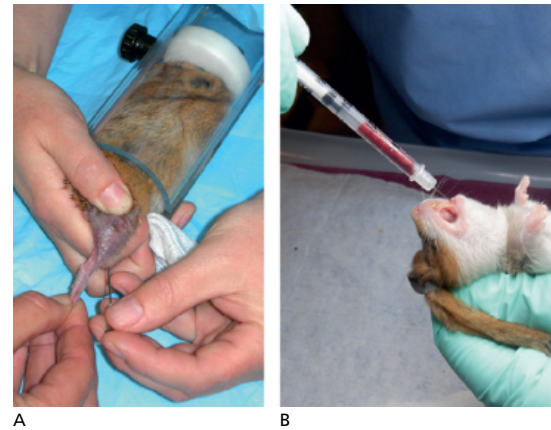
Gingival sinus puncture is also possible in guinea pigs for collection of 0.5–1 mL of blood (Figure 3.4B). Animals should be anesthetized and placed in dorsal recumbency. The lower lip is pulled back and a 27–25 gauge needle is inserted caudally at a 60° angle into the gingival midline at the base of the lower incisors to a depth of 2–4 mm, while gently aspirating.

Chinchillas

Blood can be collected from the lateral saphenous vein, femoral vein, jugular vein, gingival sinus, and cranial vena cava of chinchillas in a manner similar to the guinea pig, and with the same precautions. The jugular vein is very superficial, and the skin is thinner than in guinea pigs. Small amounts of blood can also be collected from the ventral tail artery using a 0.5 or 1 mL syringe with a 27 or 28 gauge needle. The chinchilla is restrained in an upright position against the restrainer's body, with the ventrum toward the phlebotomist. The phlebotomist holds the tail gently, by the base and in one hand, and advances the needle at a 30°–40° angle, directly on the ventral midline one-third to halfway between the base and tail tip, applying gentle suction.

Hamsters and Gerbils

Anesthesia is almost always required for blood collection in hamsters and gerbils. With practice, blood can be collected from the jugular vein by positioning the animal in dorsal recumbency, looping a length of suture around the upper incisors to assist in straightening the neck, and entering the vein from a cranial to caudal direction. Blood can be collected directly from the hub of the needle with a MHC tube. The femoral vein may also be used in much the same manner as in guinea pigs. In conscious animals, blood can be collected from the lateral saphenous vein (Figure 3.5), as described for the guinea pig, or, in hamsters, a needle can be placed in the lateral tarsal vein on the lateral aspect of the hind foot, and blood collected directly from the hub. The ventral tail artery and lateral tail vein of gerbils may also yield small amounts of blood; however, care must be taken to avoid degloving of the tail. Use of the cranial vena cava presents more risk than with larger rodents but may also be used (Figure 3.6). Collection of blood from the gingival sinus in a manner similar to guinea pigs is also very successful in hamsters and can yield up to 0.5 mL or more of blood in a very short period of time (Figure 3.5). Large volumes can be collected terminally via cardiac puncture (Figure 3.7)



A B

FIGURE 3.5. A: Collection of blood from the lateral saphenous vein of an awake hamster in a plastic restrainer. B: Gingival puncture may be used for blood collection in anesthetized hamsters.



FIGURE 3.6. Cranial vena cava puncture in an anesthetized hamster.

Rats and Mice

Lateral tail veins are easily accessed without anesthesia in rats and mice (Figure 3.8). The animal is held in the lap (for well habituated rats and mice, see RI.SE videos at https://www.ri.se/en/what-we-do/expertises/3r-focus-on-animal-welfare), a cloth can be wrapped lightly over the body or other appropriate restraint device is used, and blood is collected by direct venipuncture. When using this route, always start collection more distally on the tail and move proximally if the first attempt is unsuccessful, or if several collections are required in a relatively short time period. Doing the reverse may result

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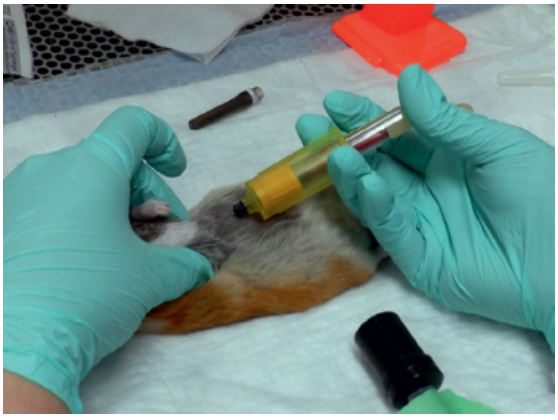
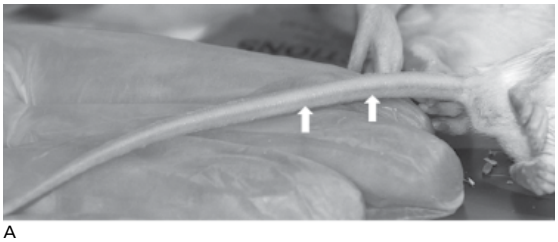
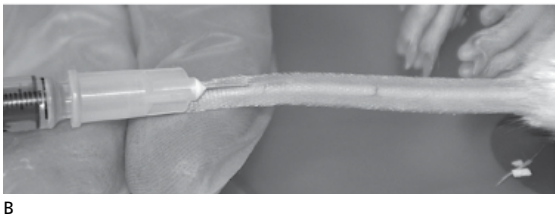


FIGURE 3.7. Large blood volumes can be collected terminally in an anesthetized hamster.



A



B

FIGURE 3.8. A: Both the mouse (depicted) and rat have ventral tail arteries that may be used for collection of small amounts of blood in a conscious animal (white arrows). Pressure must be applied for several minutes after bleeding to ensure adequate hemostasis. B: The lateral tail vein of the mouse may be used to collect small amounts of blood from a conscious animal or may be used for injection.

in hematoma formation and vessel collapse, making future attempts more difficult. Warming the animal with a heating pad or a heat lamp or immersing the tail in warm water will help vasodilate the vessels (Figure 3.9). In rats, an appropriately sized butterfly catheter with most of the tubing cut off allows the blood to drip directly into the collection tube. Puncture of the ventral tail artery in its distal half can also be performed in rats and mice by inserting a 27 gauge needle at a 30° angle to the skin and collecting blood directly from the hub with MHC tubes. Use of a small amount of topical anesthetic, such as EMLA cream, may reduce the discomfort of these procedures. The lateral saphenous vein can also be used

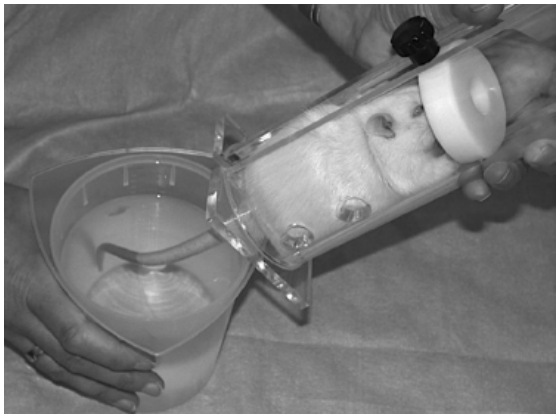


FIGURE 3.9. Vasodilatation of the tail vein may be accomplished by immersing the tail in warm water prior to bleeding. Care must be taken to ensure the water is not too hot, which may induce tissue damage.



FIGURE 3.10. Gingival blood collection from an anesthetized rat.

for blood collection as described for guinea pigs, with animals restrained carefully by hand. This is optimally a two-person procedure.

Blood collection from the gingival sinus of an anesthetized rat can yield 0.5 mL or more of blood, depending on the animal's size (Figure 3.10). In both rats and mice, blood collection from the junction of the facial vein and submandibular vein, often called mandibular or submandibular bleeding, is often used. While it does not require anesthesia, it is a blind stick and can lead to laceration of facial muscles with repeated unsuccessful attempts; thus, no more than two attempts should be made. Further, in mice, the firm restraint necessary to accomplish this procedure may lead to respiratory distress, especially for novices (Figure 3.11). To perform the technique, the mouse is very firmly grasped by the nape of the neck and the skin pulled taut so that the forelimbs are pulled back behind the head. A point at the junction of the mandible

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and a line extending from the lateral canthus of the eye (often marked by a sensory vibrissa or dimple on the side of the face) is punctured with an 18 gauge needle or 4–5.5 mm lancet, using a determined stabbing motion. The mouse is held over the collection tube, allowing the blood to drip freely until the desired amount has been collected. Release of the mouse from the restraint is usually enough to stop the bleeding. Dry gauze may be held over the site, if necessary. No more than 4–6 drops of blood should be collected from any given animal as overbleeding and shock may occur. This is diagnosed as unsteadiness and generalized pallor if the mouse is an albino. These animals should be placed in a warmed environment and treated with 1–1.5 mL of warmed lactated Ringer's solution given subcutaneously (SC) or intraperitoneally (IP). The procedure is similar in rats. The rat is scruffed tightly behind the ears and along the dorsal midline, gathering up as much loose skin as possible. In white rats, a gray dot can be found on the jaw line directly below the lateral canthus of the eye. The site of puncture is on the jaw line 0.5 cm caudal to the dot. An 18 gauge needle or 5.5–8 mm lancet is inserted deftly at a 30° angle to the skin, and the blood allowed to drip into the container. After releasing the rat, a dry gauze is pressed to the site for hemostasis.

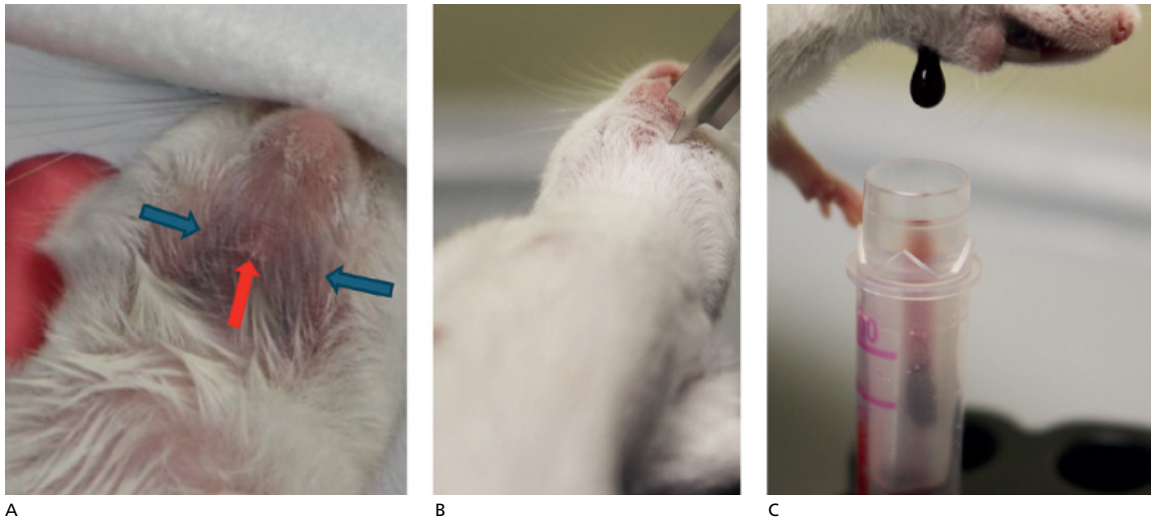


A B

FIGURE 3.11. Facial vein bleeding in a conscious mouse. A: The mouse is firmly restrained, and a needle or lancet is directed into the facial vein as demonstrated. B: After venipuncture, the mouse is held over a collection tube and the blood is allowed to drip into the tube.

In mice, a submental blood collection technique has recently been described, whereby the animal is scruffed and the head tilted back to expose the submental region (Figure 3.12). Due to the sparse hair coat under the chin, a dark spot is visible in most mice where the facial and submental veins meet. This area is punctured with a 4 or 5 mm lancet, and the blood allowed to drip into the collection tube, in a manner similar to mandibular bleeding.

With practice, jugular venipuncture can be performed in anesthetized mice and anesthetized or conscious rats. In anesthetized mice the neck must be slightly hyperextended by laying the animal in dorsal recumbency and placing a 1 mL syringe barrel or similar device under the neck or by scruffing the mouse and looping a suture around the upper incisors to pull the head back, thus extending the neck. The fur over the site is either shaved or wetted with alcohol and parted. The jugular vein appears as a blue line ~3 mm lateral to the manubrium. The vein is entered in a caudal-to-cranial direction



A B C

FIGURE 3.12. Submental vein blood collection in a conscious mouse. A: The landmarks for this technique are the whorl of hair on the mouse chin (red arrow) and lines drawn parallel to the corners of the mouth (green arrow). B: The vein is punctured with a lancet. C: The mouse is held over a container to collect the blood. Courtesy of B. Harmsen, S. Hoekwater, and A. George.

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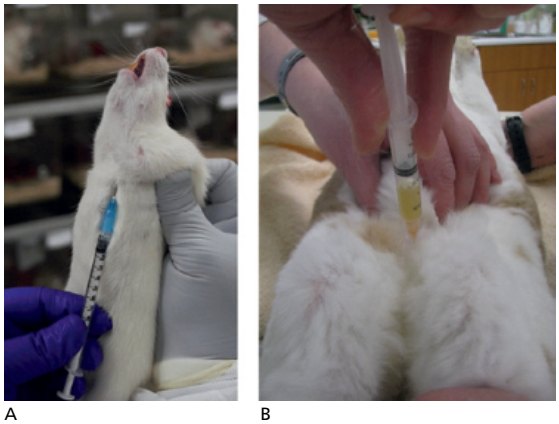
using a 0.5 mL insulin syringe with attached 28 g × ½ in needle, or a 1 mL syringe with attached 26 g × 3/8 in or detachable 27 g × ½ in needle. Blood must be withdrawn slowly to prevent collapse of the vessel. The procedure is similar in anesthetized rats, using slightly larger equipment, e.g., a 3 mL syringe case for under the neck.

Jugular venipuncture can be done with one or two people in conscious rats. For the two-person procedure, the restrainer scruffs the rat and turns their hand over so the body of the animal is lying in their palm taking care not to compress the chest. The index finger of the other hand is used to hold the head out of way, while the thumb holds the forelimbs caudally. The phlebotomist clips the area and swabs it with alcohol. The restrainer's thumb is then re-positioned slightly to apply pressure to the jugular vein just at the thoracic inlet, causing it to engorge distally. The vein should be visible as a blue line half way between the manubrium and shoulder. The phlebotomist advances a 23–25 g needle attached to a 1 mL syringe into the engorged vein while applying slight suction until blood appears in the needle, at which time the needle is held steady and blood is slowly withdrawn. If clotting is a concern, prior to venipuncture an appropriate anticoagulant, such as EDTA or heparin, can be drawn into the syringe and expelled, leaving a small volume in the hub. Once the desired amount of blood has been collected, gauze should be pressed to the site as the needle is withdrawn, and the animal held upright as soon as possible (Figure 3.13A).

Terminal Blood Collection

Cardiac Puncture

Large volumes of blood may be collected rapidly by cardiac puncture in deeply anesthetized rabbits and rodents. With the animal in dorsal recumbency, the needle is inserted into the notch formed by the last rib and the xiphoid process, and directed toward the heart at a 10–30° angle above the ventral body wall (see Figure 3.7). Mice may also be held in an upright position for this technique. Alternatively, the needle can be inserted into the lateral thoracic region toward the area of maximal heartbeat. In rats, for example, a 24 gauge 2.5 cm (1 in) needle inserted between the fifth and sixth ribs is directed at the left ventricle. In some rodents, a vacutainer tube can also be used. A direct cardiac puncture may also be performed in deeply anesthetized rodents after opening the chest cavity. Large volumes of blood can also be collected by severing the brachial vessels or by collection from the posterior vena cava.



A B

FIGURE 3.13. A: Restraint for one-handed jugular venipuncture in a conscious rat. Courtesy of J. Kylie. B: Cystocentesis collection in a rabbit. Courtesy of Calgary Avian & Exotic Pet Clinic.

Urine Collection

Rabbits

Urine samples can be collected during voluntary micturition, by housing in a metabolic cage and collecting indirectly, using direct bladder expression in the awake or anesthetized animal, via catheterization under sedation or general anesthesia, or by cystocentesis. Cystocentesis is considered the preferred method for diagnostic samples in companion rabbits, and it provides a clean and uncontaminated sample. The bladder is located just cranial to the pelvic rim and can be flaccid and difficult to palpate. Manual expression should be performed carefully as the bladder wall is thin and ruptures easily. Catheterization of both males and females is more successful if sedation (e.g., 1–2 mg/kg midazolam IM) is used. Passage of a 3.5–9 Fr catheter can be accomplished in the male rabbit by positioning the animal in a sitting position to extrude the penis. The urethral opening of the female is located on the floor of the vagina and is best accessed with the rabbit in sternal recumbency. Cystocentesis by ventral midline approach is performed using a 25–22 gauge, 2.5 cm (1 in) needle, with the rabbit held upright against the restrainer's body or in dorsal recumbency (Figure 3.13B). Ultrasound-guided cystocentesis is recommended, if available. The color of normal rabbit urine ranges from pale yellow to reddish brown, which may be confused with blood. Large amounts of crystals are normally present, such that the urine may appear opaque (Figure 3.14). Centrifugation and filtration may be necessary prior to analysis, depending on the sample. Normal urine parameters are provided below (see Urinalysis.)

Rodents

Rats and mice unaccustomed to handling often urinate upon restraint, and this response can be used to opportunistically collect a small sample into a collection tube or from a hard surface prepared for this purpose (for example, plastic wrap can be placed on a surface and droplets aspirated into a syringe). Rodents placed on a cold, clean surface will also often urinate. Manual expression in a conscious animal may result in contamination of urine with blood and should be performed cautiously to prevent bladder rupture. Manual expression or free-catch samples may contain vaginal, preputial, or environmental contaminants. Gently cleaning the perineal area before

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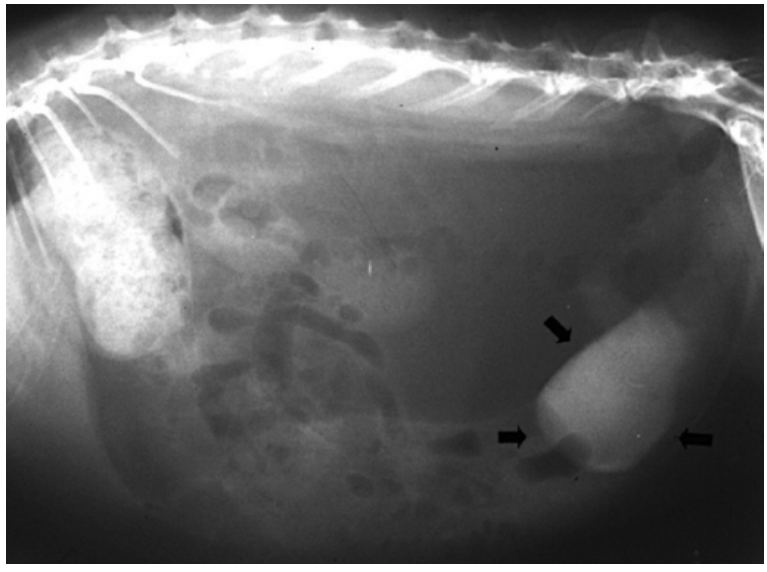


FIGURE 3.14. Rabbit urine frequently contains calcium crystals and the urinary bladder may normally appear radioopaque with survey radiographs (arrows).

collection may help minimize this contamination. Cystocentesis by ventral midline approach is the preferred method of urine collection if urine culture is intended. Sedation and use of a 25–27 g needle are recommended. Ultrasound imaging may also facilitate the procedure. If sedation is not used, restraint of the animal in an upright position against the handler's body is preferable to restraint in dorsal or lateral recumbency on an examination table. Urethral catheterization is possible in most female rodents including guinea pigs, chinchillas, rats, and mice since the urethra exits the body on an external papilla just cranial to the vulva. Ideally, animals should be anesthetized, placed in ventral recumbency, and the hindquarters elevated by the tail or propped on a roll of gauze (guinea pigs) to access this papilla. A 24 g IV catheter (with stylet removed) is used for mice, and a 3.5 Fr tomcat catheter for larger rodents. Metabolic cages are often used in research rodents for repeated urine collection.

Bone Marrow Collection

The proximal femur is the most common site for bone marrow collection in rabbits and rodents. General anesthesia is recommended for this procedure, as well as infiltration of the periosteum with a local anesthetic, taking care to adjust the dose for the size of the patient to avoid overdose. With the patient in lateral recumbency, the proximal femur is aseptically prepared, and a small incision made over the intertrochanteric fossa. A 22 g spinal needle or Jamshidi needle is inserted into the fossa through the cortical bone into the intermedullary space, by rotating back and forth. Once in place, the stylet is removed and a syringe is attached. Gentle negative pressure is applied until marrow appears in the hub. Slides are made and the sample placed in EDTA, if indicated, as soon as possible after collection to prevent clotting. Alternatively, a few drops of 10% EDTA solution can be added to the syringe before sampling. A pediatric bone marrow biopsy needle can be used to obtain core biopsy samples in a similar manner. However, once the medullary canal has been entered, the stylet is removed and the needle advanced toward the opposite cortex, where the needle is twisted slightly to free up the sample inside the needle from outside attachments. The needle is then withdrawn, and the stylet used to push the sample out the end of the needle for processing and analysis. Extramedullary hematopoiesis occurs in the liver and spleen in rabbits.

In research rabbits and rodents, bone marrow is routinely collected, usually terminally, to isolate populations of mesenchymal stem cells or dendritic cells for *in vitro* studies. A core sample may be flushed from the shaft of the femur into a collection tube with a small amount of physiologic saline solution after removing the epiphysis at each end of the bone.

Cerebrospinal Fluid Collection

Depending on bodyweight, 700–1,000 µL of fluid can be collected from the cisterna magna in rabbits. The anesthetized rabbit is positioned in lateral recumbency with the neck flexed, taking care not to obstruct the airway; intubation is recommended. After surgically preparing the site, the depression between the occipital protuberance and the atlas is palpated. A 22 gauge, 3.8 cm (1.5 in) spinal needle is carefully inserted at this site, directed toward the animal's nose. A "pop" or change in resistance is felt when the cisterna magna is entered. Fluid is allowed to drip passively into the collection tube. A lumbosacral

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approach can also be used similar to the approach in dogs. There is little information available regarding interpretation of cellular constituents of cerebrospinal fluid in rabbits; however, in one study with 20 healthy New Zealand white laboratory rabbits, a leukocyte count of ≤4 leukocytes/μL (median 1.5/μL), an erythrocyte count of 2–142 cells/μL (median 18/μL), and a protein concentration ranging from 0.13 g/L to 0.31 g/L (median 0.24 g/L) was found. Cerebrospinal fluid collection is routinely performed in research rats, and usually requires a stereotaxic apparatus and surgical pre-placement of a guide cannula in the skull.

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https://www.researchanimaltraining.com/—Research Animal Training

NORECOPA https://norecopa.no—Norwegian consensus platform for alternatives

www.nc3rs.org.uk/resource-hubs—UK National Centre for the 3Rs

https://www.ri.se/en/what-we-do/expertises/3r-focus-on-animal-welfare—Research Institute of Sweden (RI.SE)—videos demonstrating low stress handling and restraint of mice and rats during various procedures.

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HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS

Analysis of rabbit and rodent blood and urine is commonly conducted to support diagnoses and research projects. It is important to remember that hematology and clinical chemistry values may vary significantly between collection sites, and all values may vary with strain or breed of animal, nutritional status, sex, sampling site or frequency, time of day, stressors, age, disease status, environment, and drug exposure. As a consequence of these influences and others, clinical pathology reference intervals can be both broad and slightly misleading when applied to a specific population of animals or to an individual animal. However, if the practice caseload is large enough and the method of collection and analysis are consistent from patient to patient, exotic or small mammal companion practices can develop their own in-house references ranges.

Rabbits: Clinical Pathology

Most reference intervals in the literature have been developed from research studies using homogenous groups of rabbits belonging to the same breed, age, and environmental conditions. This differs from companion animals, in which a diverse group of breeds are encountered, some of which are older, on different diets (hay vs pellets), and some are possibly suffering from underlying chronic problems, such as dental disease, otitis media, and encephalitozoonosis. Increased expectations from companion animal owners and a recent emphasis on wellness examinations have enabled reference laboratories to include larger numbers of rabbits in development of normal reference intervals, which may more accurately reflect the companion small mammal population. Table 3.4 lists some normal hematology and clinical chemistry values for rabbits.

Hematology

Rabbit blood clots quickly at room temperature and must be mixed with anticoagulant without delay for whole blood analysis. Anticoagulants may alter erythrocyte and leukocyte morphology and staining characteristics. If possible, a drop of blood without anticoagulant should be used to make a peripheral blood smear for determination of differential WBC count and examination of RBC morphology. A heparinized MHC tube of blood can be used to determine the packed cell volume (PCV) and total protein. Additional blood can be placed into the appropriate tubes, e.g., purple-topped EDTA tubes and serum separator tubes, for total WBC count and clinical chemistry, taking care to avoid hemolysis.

Specific pathogen-free (SPF) New Zealand white rabbits undergo significant age-related hematology changes during the first 4 weeks of life, with a gradual increase in RBCs, WBCs, and total eosinophil and basophil counts, and a reversal of the heterophil:lymphocyte ratio to favor lymphocytes. After 6 weeks of age, these parameters become comparable to those of adult rabbits. Hemoglobin concentration peaks at 4–7 months of age, and females have significantly lower hemoglobin concentrations and lower hematocrit values than do males (mean 140 versus 127 g/L and mean 43% versus 39% for males and females, respectively). Males have higher WBC (mostly lymphocyte) populations than do female rabbits. In addition, total WBC and lymphocyte counts are lowest in the late afternoon and evening, when the heterophil and eosinophil counts rise. These variations should be kept in mind when interpreting results. There are no recognized blood groups in rabbits. Transfusions are well tolerated; however, cross-matching should be evaluated beforehand (e.g., https://eclinpath.com/hemostasis/transfusion-medicine/blood-type-incompatibility-testing).

Erythrocytes

Rabbit RBCs are biconcave discs varying in diameter from 5.0 µm to 7.8 µm. Marked anisocytosis is a normal feature, as is 2–4% reticulocytes (polychromatic erythrocytes), due to the short RBC life span (average 57 days) and subsequent high turnover. Rouleau formation and platelet clumping are commonly seen on smears. Platelets may be oblong, oval, or rounded, and from 1 µm to 3 µm in diameter. Male and older animals tend to have higher cell counts than female and younger animals. A few nucleated RBCs are normal; however, a marked increase in nucleated RBCs may indicate endothelial damage or a regenerative response. Poikilocytosis (abnormally shaped RBCs) occurs with sepsis and uremia; however, the pathophysiology underlying this change and the diagnostic and prognostic value of these findings are not entirely clear. Fragmentation of cells (schistocytes, microcytes, keratocytes, spherocytes) occurs more frequently in rabbits with inflammatory disease and malignant neoplasia than in healthy rabbits. In addition, moderate-to-marked echinocytosis is associated with renal failure and electrolyte abnormalities.

A PCV less than 30% is indicative of anemia. Regenerative anemia may be associated with trauma, flea infestation, or chronic hemorrhage secondary to conditions such as uterine adenocarcinoma. Clinically healthy rabbits mount a rapid reticulocytic response after hemorrhage. Lead toxicosis results in regenerative anemia, often with nucleated erythrocytes, hypochromasia, poikilocytosis, and cytoplasmic basophilic stippling. Nonregenerative anemia can be seen with certain conditions, such as infection, renal disease, neoplasia, or other chronic debilitating diseases. Anemia is also a common occurrence in liver lobe torsion. Dehydration is the primary reason for a PCV greater than 45% as polycythemia vera is not reported in rabbits. Cold stress in rabbits causes increases in platelet and RBC counts, PCV, and total plasma protein, and a decrease in serum albumin.

Leukocytes

Lymphocytes are the predominant WBC in healthy rabbits. Rabbit lymphocytes are similar to those of other mammals. Most circulating lymphocytes are small, measuring 7–10 µm. The less common large lymphocytes measure 10–15 µm and

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Table 3.4. Reference hematology and clinical chemistry values for rabbits (SI units are in parentheses, where appropriate).

Body weight	2–6 kg
Respiratory rate	30–60/min
Tidal volume	4–6 mL/kg
Oxygen use	0.47–0.85 mL/g/h
Heart rate	130–325/min
Blood volume	57–78 mL/kg
Blood pressure	90–130/60–90 mm Hg
Erythrocytes	4–7.2 × 10^6/mm^3 (4–7.2 × 10^{12}/L)
Hematocrit	36–48% (0.36–0.48 L/L)
Hemoglobin	10.0–15.5 g/dL (100–155 g/L)
Leukocytes	7.5–13.5 × 10^3/mm^3 (7.5–13.5 × 10^9/L)
Neutrophils	20–35%
Lymphocytes	55–80%
Eosinophils	0–4%
Monocytes	1–4%
Basophils	2–10%
Platelets	200–1,000 × 10^3/mm^3 (200–1,000 × 10^9/L)
Serum protein	2.8–10.0 g/dL (28–100 g/L)
Albumin	2.7–4.6 g/dL (27–46 g/L)
Globulin	1.5–2.8 g/dL (15–28 g/L)
Fibrinogen	0.2–0.4 g/dL (2–4 g/L)
Sodium	131–155 mEq/L (131–155 mmol/L)
Potassium	3.6–6.9 mEq/L (3.6–6.9 mmol/L)
Chloride	92–112 mEq/L (92–112 mmol/L)
Bicarbonate	16.2–38.0 mEq/L (16.2–38.0 mmol/L)
Total serum calcium	12.5–16.0 mg/dL (3.12–4.0 mmol/L)
Ionized calcium	1.5–2.2 mmol/L
Serum magnesium	2.0–5.4 mg/dL (0.82–2.22 mmol/L)
Serum phosphate	2.7–7.3 mg/dL (0.87–2.36 mmol/L)
Serum glucose	75–150 mg/dL (4.2–8.3 mmol/L)
Blood urea nitrogen (BUN)	15.0–23.5 mg/dL (5.4–8.4 mmol/L)
Creatinine	0.8–1.8 mg/dL (71–159 umol/L)
Total bilirubin	0.25–0.74 mg/dL (4–13 umol/L)
Serum lipids	280–350 mg/dL (2.8–3.5 g/L)
Phospholipids	75–113 mg/dL (0.8–1.1 g/L)
Triglycerides	124–156 mg/dL (1.4–1.8 g/L)
Cholesterol	18–35 mg/dL (0.46–0.91 mmol/L)
AST	6.5–31.0 U/L
Alkaline phosphatase	112–350 U/L
Amylase	200–500 U/L
Triiodothyronine (T3)	130–143 ng/dL (2.0–2.2 nmol/L)
Total thyroxine (TT4)	0.53–3.00 µg/dL (6.82–38.61 nmol/L)
Free thyroxine (fT4)	0.51–1.40 ng/dL (6.56–18-02 pmol/L)
Thyroid-stimulating hormone (TSH)	0.18–5.10 ng/mL

may show azurophilic cytoplasmic granules. Lymphocytes are also found in the spleen, bone marrow, lymph nodes, and the lymphatic tissues of the intestinal tract. Some causes of lymphocytosis include an immune response (such as to a virus), lymphoma, and lead toxicity.

The rabbit heterophil functions like the neutrophil of other species but is histochemically distinct. It is the second most common WBC found in peripheral blood. The heterophil measures 9–15 µm in diameter and the cytoplasm contains large, orange, nonrefractile granules against a scattering of

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smaller red-staining cytoplasmic granules. Increased neutrophils and decreased lymphocytes can be seen with prolonged stress, loud noises, and infection; with the latter, presence of bands and a left shift is uncommon.

Rabbit eosinophils stain dull pink-orange with Wright's (Romanowsky) stains and are 12–16 µm in diameter with a bilobed or horseshoe-shaped nucleus. The eosinophilic granules often completely fill the cytoplasm. Eosinophils are primarily involved in the inactivation of histamine or histamine-like toxic substances and are capable of phagocytosis. They also play a role in tissue healing. Eosinophilia may be seen with diseases of the skin, lungs, gastrointestinal tract, or uterus. Low-grade eosinophilia has also been associated with *Encephalitozoon cuniculi* infection. Healthy rabbits may have a low or absent eosinophil count.

Basophils are present in higher numbers (2–10%, and up to 30% of WBCs) than are encountered in other species, and rabbits are the only laboratory species in which peripheral basophils are seen normally in circulation. They are similar in size to heterophils, measuring 8–12 µm, and contain purple or black metachromatic granules. Their function is not fully understood. The number of circulating basophils is usually inversely proportional to that of tissue mast cells. Basophilia with concurrent eosinophilia has been described in rabbits with chronic skin problems.

Rabbit monocytes are the largest of the leukocytes. Large, dark red granules in monocyte cytoplasm have been associated with non-specific toxicity. Monocytosis is linked with chronic inflammation (abscesses, mastitis, tympanic bulla empyema); however, the absence of a monocytosis does not rule out inflammation.

Relative changes in WBC differential counts rather than changes in total WBC number are the best indication of inflammation or infectious disease in rabbits, as a leukocytosis does not typically develop. An increase in the absolute heterophil concentration and decrease in the absolute lymphocyte concentration alter the normal ratio of approximately 1 : 1 lymphocytes:heterophils. Rabbits with an acute infection may present with 60% or greater heterophils and 30% or less lymphocytes. Occasionally rabbits with an acute infectious process will have a normal differential count and a decrease in total WBC numbers. Band cells are uncommon in clinical infection, and the absence of a left shift does not rule out an infectious problem; however, leukopenia with a degenerative left shift may be seen in cases of septicemia and overwhelming bacterial infections. In rabbits experimentally infected with *Eimeria stiedae* (the agent inducing hepatic coccidiosis), anemia, leukocytosis with neutrophilia, monocytosis, and elevated levels of ceruloplasmin, transferrin, and haptoglobin were seen by the seventh day post-infection. This suggests that hepatic coccidiosis infection can be monitored with leukocyte count and serum concentrations of these plasma proteins.

Adrenocortical stress or exogenous steroids can also affect the differential count, and even restraint for clinical examination can alter the heterophil to lymphocyte ratio. An acute stress response is characterized by increased plasma cortisol concentrations and leukocytosis with heterophilia, lymphopenia, and eosinopenia. Total WBC can be used to further characterize acute stress from chronic stress, as both leukopenia and lymphopenia are more common with chronic stress. Experimentally induced viral infections cause normal-to-increased lymphocyte counts.

Coagulation

There are a variety of tests used to determine if the coagulation system is functioning normally. Bleeding time (BT) assesses platelet function and is measured by the time it takes for bleeding to stop after a standardized cut is made, usually in the buccal mucosa. In rabbits, the BT is 1.1–2.7 minutes. Prothrombin time measures the function of the extrinsic coagulation pathway and in rabbits is 7.2–7.8 seconds, depending on the method used for analysis. Activated partial thromboplastin time, a measure of the function of the intrinsic and common coagulation pathways, is approximately 35 seconds in rabbits. Thrombin time (also called thrombin clotting time), which evaluates the conversion of soluble fibrinogen to insoluble fibrin by thrombin, is 7.8–12 seconds; failure to form a clot within 10–15 seconds indicates possible fibrinogen deficiency. Normal fibrinogen concentration for rabbits is 2–4 g/L (0.2–0.4 g/dL).

Clinical Chemistry

Serum is preferred over plasma for most clinical chemistry assays, whenever possible; however, the yield for plasma is larger, requiring a smaller sample, and is more often submitted for small mammal pets. If plasma is used, heparin is the preferred anticoagulant as it has minimal or no interference with most clinical chemistry values. Blood should be allowed to clot for 30–45 minutes at room temperature prior to centrifugation.

Aspartate Aminotransferase

In rabbits, aspartate aminotransferase (AST) is widely distributed in many tissues, including cardiac muscle and liver. The half-life is only 5 hours. Elevated AST levels may be seen with liver damage, but they are not a specific hepatic marker. Hemolysis or struggling during sample collection will also elevate AST levels. Creatine phosphokinase levels also increase after restraint and are purely muscular in origin. Diarrhea is associated with increases in AST, cholesterol, phosphorus, and BUN, and decreases in serum calcium, alkaline phosphatase (ALP), total protein, glucose, and albumin. Hepatic function also may be reduced in diarrheic rabbits. Liver lobe torsion will cause an elevation of most liver enzymes including AST.

Alanine Aminotransferase

In rabbits, alanine aminotransferase (ALT) is not as useful an indicator of liver disease as for some other species because, as in other herbivores, it is not liver-specific. ALT is not affected

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by restraint. Mildly increased levels are common in apparently healthy rabbits. Mild increases have been attributed to exposure to low concentrations of toxic substances, such as resins in wood-based litter or aflatoxins in food. The half-life is approximately 5 hours.

Both ALT and AST levels increase from 8 to 36 days after experimental infection with *E. stiedae*; bilirubinemia and lipemia increase from day 22, and glycemia and total proteins decrease from days 22 to 29. Elevated ALT with concurrent elevations in ALP, bilirubin, and gamma-glutamyl transferase may be seen with hepatic lipidosis, hepatic coccidiosis, or torsion of a liver lobe.

Lactate Dehydrogenase

Lactate dehydrogenase (LDH) is produced by both muscle and liver cells and is found in high concentrations in erythrocytes. Due to its wide distribution, it is not valuable for diagnostic use in rabbits. LDH may increase with restraint or hemolysis.

Alkaline Phosphatase

ALP is found in high concentration in liver and bone and is also found in bowel epithelium, kidney tubules, and placenta. Rabbits have three known ALP isoenzymes; two produced in the liver and kidney and one produced by the intestines. Young growing animals exhibit physiologic increases in ALP activity due to osteoblastic activity. ALP is not altered by restraint, so it is a good indicator of real tissue damage. ALP does not increase due to hepatocellular damage; however, bile stasis caused by conditions such as hepatic coccidiosis, liver abscesses, liver lobe torsion, neoplasia, or lipidosis will elevate ALP. ALT, bilirubin, and GGT are also usually elevated with these conditions. Elevated ALP is also seen with bone lesions in rabbits.

Creatine Kinase (Creatine Phosphokinase)

Creatine kinase (CK) is commonly increased in the serum of rabbits due to physical restraint and phlebotomy. It is a rapid and sensitive indicator of muscle degeneration, and precedes histologic changes in the muscle by up to 3 days. It increases more rapidly and to a greater extent than AST and LDH in rabbits undergoing surgery. This enzyme may also increase with myopathies.

Gamma Glutamyl Transferase

Gamma glutamyl transferase (GGT) activity is low in rabbit serum. Activity of this enzyme is high in the kidney but doesn't reach the circulation because it is eliminated in the urine. Elevated GGT in rabbits is often linked to obstructive lesions of the bile ducts but with a lower sensitivity than for other species.

Bile Pigments

Rabbits produce a large quantity of bile for their weight, and the main component is biliverdin. Biliverdin cannot be directly assayed. Approximately 30% of biliverdin is converted to bilirubin, which can be measured in the blood. The main cause of elevated levels of bilirubin is bile flow obstruction, which can be seen with hepatic coccidiosis, especially in young rabbits, biliary neoplasia, hepatic lipidosis, or liver lobe torsion. Aflatoxicosis from eating moldy food may cause hepatic fibrosis with increased bilirubin and ALT levels. Viral hemorrhagic disease causes marked acute hepatic necrosis and increased bilirubin, concurrent with high levels of all hepatocellular enzymes.

Bile Acids

Bile acids are used as a measure of liver function in other species by comparing fasting and postprandial levels. Cecotrophy makes it difficult to obtain a fasted blood sample in rabbits, and because of this bile acid measurement is not a routine procedure in clinical practice.

Cholesterol and Triglycerides

Cholesterol is either synthesized in the liver or obtained from the diet and is a necessary precursor of steroid molecules. It is metabolized by the liver and excreted in the bile. Fasting is needed for accurate measurement, which limits its diagnostic value in rabbits because of cecotrophy. Abnormal levels of cholesterol and triglycerides (TG) can be related to a diet rich in fats, obesity, or hepatic disease. In anorexic rabbits, elevated cholesterol carries a poor prognosis, because it indicates end-stage hepatic lipidosis. Elevated cholesterol has also been linked to sepsis, pancreatitis, diabetes mellitus, nephrotic syndrome, and chronic renal failure. Decreased serum cholesterol can be seen with liver failure or malnutrition. The rabbit is often used as a model for cholesterol metabolism since high-cholesterol diets are very effective at producing hypercholesterolemia in this species. Certain strains of rabbits, such as the Watanabe heritable hyperlipidemic (WHHL) and Saint Thomas strains, normally have high blood cholesterol and lipids. Recently, models of hypertriglyceridemia have been produced by mating WHHL rabbits with normal Japanese White rabbits (TGH and PHT strains).

Amylase and Lipase

Amylase is derived almost exclusively from the pancreas in rabbits, and elevated levels indicate damage from pancreatitis, pancreatic duct obstruction, peritonitis, or abdominal trauma. Renal failure results in elevated levels because the enzyme is cleared by renal filtration. The half-life of amylase in rabbits is 97 minutes. Corticosteroids can increase serum amylase concentration while hemolysis decreases levels. The function and diagnostic value of lipase in rabbits are unknown; like amylase, it is elevated by corticosteroid administration.

Blood Urea Nitrogen and Creatinine

Urea is produced from protein catabolism and is excreted by the kidneys. BUN levels in rabbits are dependent on a number of factors, including circadian rhythm, amount and type of

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protein in the diet, nutritional status, liver function, intestinal absorption, urease activity of cecal flora, and hydration status. Small changes in urea levels are often hard to interpret, and mild elevations in BUN are a common finding. Elevated BUN may be caused by obstructed urine flow due to urolithiasis or renal tumors. BUN levels below the lower reference limit may indicate hepatic insufficiency or muscle mass loss.

Creatinine levels may be a more reliable indication of renal function than BUN in the rabbit, as they are not influenced by nonrenal factors. Rabbits have a limited ability to concentrate urine, and diarrhea or only a few hours without drinking may cause an increase in urea and creatinine levels suggestive of pre-renal azotemia. Levels rapidly return to normal once dehydration is corrected. Prerenal azotemia can occur with stress, fright, water deprivation, dehydration, heat stroke, toxic insults, and gastrointestinal hemorrhage due to increased protein digestion. In most cases of prerenal azotemia, elevations of BUN are less than 0.0555 mmol/L (100 mg/dL) and are accompanied by urine-specific gravity values greater than 1.030.

Renal azotemia, in association with hyper- or hypokalemia, hypercalcemia, hyperphosphatemia, metabolic acidosis, nonregenerative anemia, and isosthenuric urine, can be seen with clinical *E. cuniculi* infection, chronic interstitial nephritis, glomerulonephritis, pyelonephritis, nephrolithiasis, renal cysts, and lymphosarcoma. Variable increases in BUN and creatinine levels occur with isosthenuric urine. Levels of serum urea and creatinine do not increase until approximately 75% of renal function has been lost, making early diagnosis of renal disease difficult.

Postrenal azotemia can occur with obstruction of urine flow due to bladder sludge or urolithiasis, and urine-specific gravity will vary with these conditions. Abdominal radiography is recommended in all azotemic rabbits.

Glucose

Due to their pattern of eating many small meals throughout the day, glucose metabolism in rabbits differs from that in dogs or cats. In addition, rabbits use volatile fatty acids produced in the cecum as their primary source of energy. Because rabbits continue to ingest cecal pellets when food is withdrawn, a fasting blood sample is difficult to obtain. Diabetes mellitus is rare in rabbits. Clinical signs include polydipsia, polyuria, polyphagia, very high blood glucose levels and glucosuria. In clinical practice, most cases of hyperglycemia are caused by stress from transport, handling, blood collection, or from underlying disease. Concomitant glucosuria may also occur. Other causes of hyperglycemia include acute intestinal obstruction, early mucoid enteropathy, hepatic lipidosis, hypovolemic shock, hyperthermia, stress, exogenous glucocorticoids, and other drugs such as isoflurane and xylazine. The degree of hyperglycemia may also have prognostic values in acute gastric obstructions.

Hypoglycemia may be seen with prolonged anorexia and metabolism of adipose tissue, which predisposes to hepatic lipidosis. It may also occur in young rabbits, acute sepsis or terminal mucoid enteropathy, liver failure, or other chronic disease. Blood samples that sit at room temperature for too long may result in low glucose levels.

Electrolytes

Rabbits are susceptible to electrolyte imbalances due to their complex gastrointestinal physiology combined with the limited ability of their kidneys to correct acid–base shifts. With few exceptions, any abnormalities in serum electrolytes should be fully investigated to rule out diseases of the gastrointestinal or renal system. Anorexia rapidly leads to metabolic acidosis.

Sodium levels have low diagnostic value in rabbits. Hypernatremia may be due to dehydration or loss of fluids due to diarrhea, peritonitis, burns, or myiasis. True hyponatremia may be associated with polyuric renal failure. Hyponatremia has been associated with increased mortality risks in hospitalized rabbits. Lipemia or hyperproteinemia can artifactually decrease sodium levels.

Hypoadrenocorticism has not been reported in rabbits. Elevated potassium levels are more often due to acute kidney injury or urine flow obstruction. Severe tissue damage may also cause hyperkalemia, while hemolysis can artifactually elevate levels. Metabolic acidosis indirectly results in hyperkalemia due to increase in exchange of potassium ions cross the cell membrane.

Hypokalemia in rabbits can be caused by dietary insufficiency and loss of fluids from the gastrointestinal system or kidneys. Stress-induced increases in catecholamines can also cause hypokalemia. Hyperproteinemia and lipemia may artifactually decrease blood potassium levels and affected animals may present with muscle weakness.

Chloride levels in rabbits may increase with dehydration or increased dietary salt intake, and decrease with diarrhea or low dietary salt intake. Hypochloremic metabolic alkalosis should raise a strong suspicion of gastric obstruction.

Calcium metabolism in rabbits is different than in other mammalian species. Blood calcium levels are influenced more by the calcium content of the diet than in other mammals. Rabbits absorb calcium in proportion to the concentration of the ion in the gut and the kidney eliminates the excess. Vitamin D is not important in intestinal calcium absorption if dietary levels are high, yet it does play a role if levels are low and is important in calcium distribution throughout the body. Parathyroid hormone regulates blood calcium levels, but the level at which calcium is moved from blood to bone is high in the rabbit, and total blood calcium levels are higher and the range is broader than in other species. The urinary excretion rate of calcium is approximately 45–60%, whereas most mammals excrete no more than 2% of their calcium through renal filtration. This predisposes the rabbit to accumulation of calcium precipitates in the bladder (urine sludge) as well as urolithiasis in kidneys, ureters, and bladder. Renal failure compromises calcium excretion but

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not absorption, resulting in hypercalcemia in conjunction with clear urine. Excessive mineralization of bones and kidneys and calcification of the aorta are often seen in rabbits with chronic renal failure. Another differential diagnosis for ectopic mineralization is hypervitaminosis D. Measurement of blood calcium is essential to diagnose renal disease in rabbits, which carries a poor prognosis. The most common cause of hypercalcemia in companion rabbits is excessive dietary calcium. Thymoma may also produce paraneoplastic hypercalcemia. Hypocalcemia is rarely reported in rabbits and can be caused by hypoalbuminemia due to poor nutrition. Young rabbits and pregnant does have a higher calcium requirement than normal adult rabbits. Hypocalcemic seizures have been reported in late pregnant and lactating does. Rabbits normally have higher plasma ionized calcium than most other mammals (up to 1.7–1.8 mmol/L).

Phosphorus is intracellular and blood phosphorus levels are readily increased by hemolysis. Blood phosphate levels should always be evaluated with calcium to determine the mineral balance in patients diagnosed with urinary calculi, dental disease, or nutritional secondary hyperparathyroidism. The kidney is the primary organ involved in phosphorus balance through regulation of glomerular filtration and tubular reabsorption, so blood phosphate levels can be used as an indirect measurement of kidney function and general azotemia. Serum phosphorus levels can be elevated as a result of prerenal, renal, or postrenal effects. Hyperphosphatemia usually indicates chronic kidney failure with a loss of >75% of nephrons and may also be an indicator of soft tissue trauma. The clinical significance of hypophosphatemia is not known.

Magnesium levels in rabbits may increase with dehydration, hyperthyroidism, tissue trauma, or adrenocortical insufficiency.

Total Thyroxine, Free Thyroxine, and Thyroid-Stimulating Hormone

Thyroid diseases are rare in rabbits and signs are nonspecific. Published reference values for thyroid hormones vary greatly depending on the site of testing and methodology used for analysis. In general, levels determined using radioimmunoassay (RIA) are much higher than those using chemiluminescence assay (CLIA). In addition, published values often refer to research rather than companion rabbit settings, the latter including more breeds and older animals. Care must be taken when interpreting results as various unrelated diseases can affect thyroid hormone levels (i.e., nonthyroidal illness syndrome), which may lead to misdiagnoses. Circulating free thyroxine levels (fT4) are less likely to be affected by nonthyroidal illness syndrome. TSH reference values are useful in differentiating between thyroid diseases and nonthyroidal illness.

Values for total thyroxine (TT4), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) in a large number of unanesthetized companion rabbits using CLIA (for TT4, fT4) and enzyme-linked immunosorbent assay (ELISA) (for TSH) have recently been established to assist with diagnosing thyroid disease. For accuracy, species-specific kits were found to be necessary to measure TSH in rabbits, whereas TT4 and fT4 could be measured using standard CLIA methods developed for dogs. In rabbits, TT4 was found to decrease linearly with age; however, neither fT4 nor TSH were negatively correlated to age. Reference values from this study are included in Table 3.4.

Protein Disorders

Albumin cannot be reliably measured using standard analyzers in rabbits, it needs to be evaluated via protein electrophoresis. The primary cause of hyperproteinemia in rabbits is dehydration, but it can also occur secondary to chronic infectious or metabolic processes. Hypoproteinemia is usually attributable to chronic malnutrition or protein loss. If both albumin and globulin are low, hemorrhage or protein loss through exudative skin lesions, such as burns or primary or secondary myiasis, should be considered. The liver is the only site of albumin synthesis, so hypoalbuminemia may indicate an advanced hepatic disease, such as may result from hepatic coccidiosis or fibrosis and necrosis secondary to migration of *Cysticercus pisiformis* (the larval form of *Taenia pisiformis* tapeworm). A common cause of hypoalbuminemia in companion rabbits is chronic malnutrition either from poor diet or advanced dental disease. Reduced cecotrophy due to obesity, trauma, chronic pain or other chronic illness, or dental disease will also cause hypoproteinemia.

Division of globulins into distinct fractions using serum or plasma electrophoresis provides additional information. Plasma is preferable for this analysis since it contains fibrinogen, which is an acute phase protein. Elevated levels of alpha globulins may occur with acute disease such as bacterial infection or abscess. Beta globulins consist of several acute phase proteins, including fibrinogen. Fibrinogen may be associated with inflammation in rabbits; however, the correlation is not as clear as for other species. Elevated gamma globulins, which consist primarily of antibodies, indicate a subacute-to-chronic inflammation, especially in the presence of a bacterial infection. Coronavirus infections lead to a significant increase in rabbit globulins similar to that seen in cats.

Urinalysis

Rabbits urinate infrequently but in large volumes, averaging 130 mL/kg/day (range 20–350). Normal rabbit urine is turbid and rich in minerals, and it requires centrifugation or filtration for biochemical analysis or examination. Suckling rabbits and lactating does have clear urine, indicative of low excretion of calcium. Clear urine may also be seen with renal failure. The normal color may range from light yellow to reddish-brown, because of dietary pigments. Porphyrinuria should be distinguished from hematuria, which can be seen with cystitis, urolithiasis, and uterine bleeding due to uterine adenocarcinoma,

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uterine polyps, endometrial hyperplasia, abortion, or ruptured uterine venous aneurysms. Urine preserved by refrigeration is suitable for examination for up to 2–3 hours.

Urine test dipsticks work well to evaluate blood, glucose, ketone, and pH levels in rabbit urine but are not accurate for other parameters. Trace protein and a few RBCs or WBCs are common. Stress hyperglycemia may cause glucosuria. True glucosuria may indicate hepatic lipidosis (common in obese rabbits) or, rarely, diabetes mellitus. The presence of ketones in the urine is always abnormal and may be due to anorexia, hepatic lipidosis, pregnancy toxemia, or diabetes mellitus. Urine pH tends to be high (7.5–9) in rabbits fed an appropriate diet. Acidic urine indicates acidosis due to anorexia, fever, pregnancy toxemia, or hepatic lipidosis.

The specific gravity (SG) of normal rabbit urine is often quite low, with an average of 1.015 (range 1.003–1.036). Prerenal azotemia is associated with an elevated SG (>1.030), whereas true azotemia due to renal failure is associated with dilute urine (SG < 1.013).

Trace protein in the urine of clinically normal rabbits is not significant, but dilute urine (SG < 1.020) with protein is highly significant. Proteinuria appears earlier than other biochemical changes in renal disease, making this test useful in clinical practice. The normal ratio of urine protein : urine creatinine is less than 0.6. Sediment examination can differentiate normal urine that is rich in crystals from abnormal crystalluria.

Cytology is similar to that for other mammals, and a small number of leukocytes are considered normal. Gram or trichrome stains on urinary sediment can reveal *E. cuniculi* spores.

Small Rodents: Clinical Pathology

The extensive use of small rodents in biomedical research has allowed clinically useful information to become available to small mammal veterinary practitioners. As standards of veterinary care are constantly rising for companion animals, rodent owners are also expecting higher levels of medicine and surgery. Tables 3.5–3.10 give normal hematology and clinical chemistry values for guinea pigs, chinchillas, hamsters, gerbils, mice, and rats, respectively.

Hematology

Erythrocytes

Similar to rabbits, the RBCs of most small rodents have a short half-life compared with larger domestic mammals, ranging from 45 to 68 days. Polychromasia is commonly observed. Guinea pigs and chinchillas have larger RBCs compared with other small rodents. Rouleau formation and polychromasia are more common in very young animals. Polychromasia and macrocytosis are characteristic of regenerative anemias. There is no significant difference between male and female guinea pig RBCs and hemoglobin levels. Blood samples taken from chinchillas anesthetized with ketamine and xylazine may demonstrate an increased PCV, hemoglobin, mean corpuscular hemoglobin concentration (MCHC), and WBC, and a decreased monocyte, basophil, and eosinophil count than samples taken from awake animals.

Newborn hamsters may have up to 10–30% nucleated erythrocytes, while adults have 2% or fewer. RBC levels decrease after castration. Erythrocyte values increase during estivation, perhaps due in part to an extended RBC lifespan.

Red cell life span in the gerbil is approximately 9–10 days, which is short compared with that of other small rodents. This may result in up to 40% of circulating RBCs with stippling as well as the presence of reticulocytes in healthy, young gerbils, and lower levels of both in adults.

In rats and mice, Howell–Jolly bodies (small peripheral bodies seen within the RBC caused by basophilic nuclear remnants) are common in small numbers of RBCs, and rouleau formation is rarely seen. The mouse RBC has a life span of approximately 40–47 days.

In rats, hematology values vary depending on the site of blood withdrawal. For example, PCV, hemoglobin (Hb), and WBCs are increased in tail vein blood samples compared with blood obtained by cardiac puncture, likely due to decreased flow rates and sludging of blood through smaller vessels in the tail. All can be considered within normal range, but this emphasizes the need to use consistent sampling sites, in clinic and in studies, whenever possible. RBCs are smaller in rats compared with rabbits and guinea pigs, and reticulocyte levels are relatively high in young rats and then decrease, although polychromasia remains a constant feature throughout a rat's life. Other hematology changes that occur as rats age include increases of Hb, RBC, and PCV levels from 2 to 8 weeks, and decreases to a stable level at 8 weeks of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and reticulocytes. Reticulocyte numbers increase and MCHC decreases between 66 and 121 weeks, and neutrophils and lymphocytes increase between 66 and 121 weeks. The hematocrit is not an accurate indicator of blood loss because fluid dilution of the cell component is not complete for up to 72 hours after blood collection. RBC life span in rats is approximately 45–68 days.

Leukocytes

The function of small rodent neutrophils is similar to that of other mammals, although it may differ in cytochemistry and ultrastructure. For example, hamster neutrophils have no lysozyme activity and mouse neutrophils have decreased ALP activity, compared with other mammalian neutrophils. Neutrophils of most small rodents except rats and mice are referred to as heterophils because their granules are eosinophilic in color with Romanowsky stains. As for other mammals, the nucleus may be segmented or band-shaped (immature).

Guinea pig heterophils contain round granules, and the nucleus may normally be segmented or band-shaped. In sows, sex chromatin lobes ("drumsticks" or Barr bodies) may be

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Table 3.5. Reference hematology and clinical chemistry values for guinea pigs (SI units are in parentheses, where appropriate).

Body weight	700–1,200 g
Respiratory rate	40–130/min
Tidal volume	2.3–5.3 mL/kg
Heart rate	230–380/min
Blood volume	65–85 mL/kg
Blood pressure	80–94/55–58 mmHg
Erythrocytes	$4.5–7.0 \times 10^6/mm^3$ ($4.5–7.0 \times 10^{12}/L$)
Hematocrit	37–48% (0.37–0.48 L/L)
Hemoglobin	11–15 g/dL (110–150 g/L)
Leukocytes	$7–18 \times 10^3/mm^3$ ($7–18 \times 10^9/L$)
Neutrophils	28–44%
Lymphocytes	39–72%
Eosinophils	1–5%
Monocytes	3–12%
Basophils	0–3%
Platelets	$250–850 \times 10^3/mm^3$ ($250–850 \times 10^9/L$)
Serum protein	4.6–6.2 g/dL (46–62 g/L)
Albumin	2.1–3.9 g/dL (21–39 g/L)
Globulin	1.7–2.6 g/dL (17–26 g/L)
Sodium	132–156 mEq/L (132–156 mmol/L)
Potassium	4.5–8.9 mEq/L (4.5–8.9 mmol/L)
Chloride	98–115 mEq/L (98–115 mmol/L)
Serum calcium	5.3–12 mg/dL (1.32–3.00 mmol/L)
Serum phosphate	3.0–12 mg/dL (0.97–3.87 mmol/L)
Serum glucose	60–125 mg/dL (3.3–6.9 mmol/L)
BUN	9.0–31.5 mg/dL (3.2–11.2 mmol/L)
Creatinine	0.6–2.2 mg/dL (53–194 umol/L)
Total bilirubin	0.3–0.9 mg/dL (5–15 umol/L)
Serum lipids	95–240 mg/dL (1.0–2.4 g/L)
Phospholipids	25–75 mg/dL (0.3–0.8 g/L)
Triglycerides	0–145 mg/dL (0–1.4 g/L)
Cholesterol	20–43 mg/dL (0.52–1.11 mmol/L)
ALT	10–25 IU/L
Alkaline phosphatase	18–28 IU/L
Total thyroxine (TT4)	0.50–3.60 µg/dL (6.44–46.33 nmol/L)
Free thyroxine (fT4)	0.57–1.90 ng/dL (7.34–24.45 pmol/L)
Thyroid-stimulating hormone (TSH)	0.58–8.14 ng/mL

seen occasionally in the heterophil nucleus. Chinchilla heterophils usually exhibit a hypersegmented nucleus. The nuclei of mature gerbil, rat, and mouse granulocytes may lack distinct lobes and be horseshoe-, sausage-, or donut-shaped. Rats and mice have neutrophils with colorless cytoplasm, although some fine red granules may be present such that the cytoplasm is diffusely eosinophilic with Romanowsky stains.

Eosinophils make up 1–9% of total leukocytes in small rodent blood and contain large cytoplasmic granules that become increasingly eosinophilic as the cell matures. Eosinophils increase in number when there is a chronic antigenic stimulus such as occurs with parasite larva and allergic reactions associated with mast cells and basophilic degranulation. In rats, *Trichosomoides crassicauda*, a urinary bladder nematode, may induce a peripheral eosinophilia. Eosinophils may be distinguished from heterophils and neutrophils by their larger size, round-to-rod-shaped granules, pale basophilic cytoplasm, and ring- or U-shaped nucleus. In chinchillas, eosinophils are the only granulocyte with eosinophilic cytoplasmic granules.

Rodent basophils make up 0–4% of total leukocytes and have characteristic reddish-purple to black staining granules on Romanowsky-stained films. Morphologically, granules of rodent basophils are homogeneous. The basophils of rodents must be differentiated from mast cells, which are more common in the sample when blood is taken by cardiac puncture.

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Table 3.6. Reference hematology and clinical chemistry values for chinchillas (SI units are in parentheses, where appropriate).

Body weight	450–800 g
Respiratory rate	40–80/min
Heart rate	40–100/min
Erythrocytes	5.2–10.7 × 10^6/mm^3 (5.2–10.7 × 10^{12}/L)
Hematocrit	27–54% (0.27–0.54 L/L)
Hemoglobin	8–15.4 g/dL (80–154 g/L) [33 9]
Leukocytes	4–11.5 × 10/mm(4–11.5 × 10/L)
Neutrophils	9–45%
Lymphocytes	19–98%
Eosinophils	0–9%
Monocytes	0–6%
Basophils	0–1%
Platelets	254–740 × 10^3/mm^3 (254–740 × 10^9/L)
Serum protein	5.0–6.0 g/dL (50–60 g/L)
Albumin	2.4–4.2 g/dL (24–42 g/L)
Sodium	130–155 mEq/L (130–155 mmol/L)
Potassium	5–6.5 mEq/L (5–6.5 mmol/L)
Chloride	105–115 mEq/L (105–115 mmol/L)
Serum calcium	5.6–12.1 mg/dL (1.40–3.02 mmol/L)
Serum phosphate	4–8 mg/dL (1.29–2.58 mmol/L)
Serum glucose	60–120 mg/dL (3.3–6.7 mmol/L)
BUN	10–25 mg/dL (3.6–8.9 mmol/L)
Total bilirubin	0.4 mg/dL (7 umol/L)
Cholesterol	40–100 mg/dL (1.03–2.59 mmol/L)
AST	96 IU/L
ALT	10–35 IU/L
Alkaline phosphatase	3–47 IU/L

Monocytes are the largest leukocyte in peripheral blood films and are similar in all small rodents. The nuclei vary from round to oval to lobed. The cytoplasm is moderately abundant, pale blue-gray, and may contain azurophilic granules.

Lymphocyte morphology is variable in small rodents with respect to size, cytoplasmic color (pale to dark basophilia), and degree of nuclear chromatin condensation. The size falls between that of an RBC and a neutrophil. Smaller cells are thought to be inactive. Reactive lymphocytes have more abundant cytoplasm with deeper basophilic staining and nuclei with clefts. These cells are thought to be B cells involved in immunoglobulin production.

Both large and small lymphocytes are present normally in guinea pigs. The distinctive Foa–Kurloff or Kurloff cell is a large lymphocyte containing a single large intracytoplasmic inclusion 1–8 µm in diameter referred to as a Kurloff body (see Figure 2.36). They are more common in sexually immature male and pregnant guinea pigs, suggesting that their presence is influenced by sex hormones. These cells are thought to function as natural killer (NK) cells, a type of lymphocyte. Kurloff cells may be found in the peripheral circulation as well as in fixed tissue sections, for example, spleen, and should not be misinterpreted as neoplastic cells. In female rats, removal of the ovaries and to a lesser extent the uterus increases circulating T and B lymphocyte numbers in peripheral blood.

In general, the differential WBC count of rodents tends to be predominantly lymphocytic. The WBC response to disease tends to result in an increase in immature leukocytes, toxic neutrophils, and Dohle bodies (aggregates of endoplasmic reticulum that appear as gray-blue cytoplasmic inclusions) rather than increases in the total and differential leukocyte counts. Leukocytosis in small rodents may be associated with chronic, closed-cavity inflammation, such as abscesses. Epinephrine induces neutrophils to leave the marginating pool in response to the increased heart rate and blood flow, resulting in a neutrophilia. Exogenously administered corticosteroids as well as increased circulating endogenous corticosteroids associated with physiological stress will result in lymphopenia, and occasionally, a mature neutrophilia. In hamsters, the WBC counts decrease during estivation.

WBC count can be estimated from a well-prepared smear of fresh blood. The numbers of WBCs per high-power (×40) objective from at least five fields are counted. The average number is multiplied by 1,000 to give an estimated total WBC.

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Table 3.7. Reference hematology and clinical chemistry values for hamsters (SI units are in parentheses, where appropriate).

Body weight	85–150 g
Respiratory rate	35–135/min
Tidal volume	0.6–1.4 mL
Oxygen use	0.6–1.4 mL/g/hr
Heart rate	250–500/min
Blood volume	65–80 mL/kg
Blood pressure	150/100 mmHg
Erythrocytes	$6–10 \times 10^6/mm^3$ ($6–10 \times 10^{12}$/L)
Hematocrit	36–55% (0.36–0.55 L/L)
Hemoglobin	10–16 g/dL (100–160 g/L)
Leukocytes	$3–11 \times 10^3/mm^3$ ($3–11 \times 10^9$/L)
Neutrophils	10–42%
Lymphocytes	50–94%
Eosinophils	0–4.5%
Monocytes	0–3%
Basophils	0–1%
Platelets	$200–500 \times 10^3/mm^3$ ($200–500 \times 10^9$/L)
Serum protein	4.5–7.5 g/dL (45–75 g/L)
Albumin	2.6–4.1 g/dL (26–41 g/L)
Globulin	2.7–4.2 g/dL (27–42 g/L)
Sodium	128–144 mEq/L (128–144 mmol/L)
Potassium	3.9–5.5 mEq/L (3.9–5.5 mmol/L)
Serum calcium	5–12 mg/dL (1.25–3.00 mmol/L)
Serum phosphate	3.4–8.2 mg/dL (1.10–2.65 mmol/L)
Serum glucose	60–150 mg/dL (3.3–8.3 mmol/L)
BUN	12–25 mg/dL (4.3–8.9 mmol/L)
Creatinine	0.91–0.99 mg/dL (80–88 umol/L)
Total bilirubin	0.25–0.60 mg/dL (4–10 umol/L)
Cholesterol	25–135 mg/dL (0.66–3.49 mmol/L)
AST	28–122 IU/L
ALT	22–128 IU/L
Alkaline phosphatase	45–187 IU/L

Clinical Chemistry

Small rodent clinical chemistry interpretation does not differ greatly from that of rabbits. In guinea pigs and rats, ALT has little organ specificity, but it may still be useful for assessing liver damage. In mice, ALT has the highest activity in the liver, and increased levels of ALT are attributable to hepatic injury. AST is nonspecific in mice. Fasted rats may exhibit a marked increase (five- to sevenfold) in hepatic-origin ALT, which may also increase in response to handling or liver disease. ALP in healthy hamsters is composed mostly of the isoenzyme from bone and intestine. Elevated levels may be seen in hamsters with liver disease, but dramatic increases are usually associated with bile duct obstructions. High levels of ALP are also associated with leukemia and prostatic tumors. The guinea pig liver contains higher levels of GGT compared with other small rodents.

Unlike in the rabbit, bilirubin is the end-product of hemoglobin metabolism in small rodents, and total bilirubin levels are a sensitive indicator of liver damage or hemolysis in these animals.

High serum cholesterol levels develop in gerbils even when they are fed diets that contain normal levels of fat. Gerbils have higher serum lipid values than other small rodents and lipemia is common.

BUN levels are highly variable in small rodents and may be affected by diet. Creatinine levels may be influenced by the assay method. Picric acid–based tests, which are commonly used in automated assays, may overestimate creatinine levels in small rodents, necessitating the use of alternate methods for accurate determinations (i.e., high-performance liquid chromatography). In hamsters, high-protein diets (20% or more) may be accompanied by elevated BUN levels. In mice, significant

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Table 3.8. Reference hematology and clinical chemistry values for gerbils (SI units are in parentheses, where appropriate).

Body weight	55–100 g
Respiratory rate	90/min
Oxygen use	1.4 mL/g/hr
Heart rate	360/min
Blood volume	65–80 mL/kg
Erythrocytes	8–9 × 10 ^{6}/mm^{3} (8–9 × 10^{12}/L)
Reticulocytes	21–54/1,000 RBC
Stippled RBC	2–16/1,000 RBC
Polychromatophilic RBC	5–30/1,000 RBC
Hematocrit	43–49% (0.43–0.49 L/L)
Hemoglobin	12.6–16.2 g/dL (126–162 g/L)
Leukocytes	7–15 × 10^{3}/mm^{3} (7–15 × 10^{9}/L)
Neutrophils	5–34%
Lymphocytes	60–95%
Eosinophils	0–4%
Monocytes	0–3%
Basophils	0–1%
Platelets	400–600 × 10^{3}/mm^{3} (400–600 × 10^{9}/L)
Serum protein	4.3–12.5 g/dL (43–125 g/L)
Albumin	1.8–5.5 g/dL (18–55 g/L)
Globulin	1.2–6.0 g/dL (12–60 g/L)
Sodium	144–158 mEq/L (144–158 mmol/L)
Potassium	3.8–5.2 mEq/L (3.8–5.2 mmol/L)
Serum calcium	3.7–6.2 mg/dL (0.92–1.55 mmol/L)
Serum phosphate	3.7–7.0 mg/dL (1.19–2.26 mmol/L)
Serum glucose	50–135 mg/dL (2.8–7.5 mmol/L)
BUN	17–27 mg/dL (6.1–9.6 mmol/L)
Creatinine	0.6–1.4 mg/dL (53–124 umol/L)
Total bilirubin	0.2–0.6 mg/dL (3–10 umol/L)
Cholesterol	90–150 mg/dL (2.38–3.88 mmol/L)

increases in BUN occur when the host has lost approximately 70% of renal function.

Glucose levels are affected by the nutritional, hormonal, and affective state of the animal. Hyperglycemia has been reported in hamsters during estivation. Administration of thiobarbiturates may also lead to hyperglycemia. Several cases of insulinoma have been reported in guinea pigs.

Amyloidosis, a condition common to hamsters, mice, gerbils, and guinea pigs, is associated with decreased plasma albumin and increased globulin levels. In mice and rats, hyperproteinemia occurs with dehydration, whereas hypoproteinemia (hypoalbuminemia) occurs with chronic renal disease.

Hyperthyroidism is not uncommon in companion guinea pigs and may be underdiagnosed. Clinical signs can include polyuria, polydipsia, polyphagia with weight loss, alopecia, loss of nails, dental lesions, and a palpable mass in the neck. Published reference values for thyroid hormones are available in the literature but vary greatly depending on the laboratory and methodology used for analysis. In a study of 109 guinea pigs (62 laboratory and 47 companion), using a point-of-care enzyme immunoassay (EIA) to measure total thyroxine (TT4), overall mean plasma TT4 was determined to be 4.04 g/dL, with values of 4.17 g/dL in the laboratory animal group and 3.88 g/dL in the companion animal group. Sex, housing type, sampling protocol, and age had no significant effect on values, although younger guinea pigs tended to have higher average levels than older ones.

In another study, values for TT4, free thyroxine (fT4), and TSH in a large number of awake companion guinea pigs using CLIA (for TT4, fT4) and ELISA (for TSH) were established to assist with diagnosing thyroid disease in these animals. For accuracy, species-specific kits were found to be necessary to measure TSH, whereas TT4 and fT4 were able to be measured using standard CLIA methods used for dog samples. This study also demonstrated that TT4 values tended to decrease in older animals. Reference values from this study are included in Table 3.5. Levels determined using RIA, in general, are much higher than those using CLIA.

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Table 3.9. Reference hematology and clinical chemistry values for mice (SI units are in parentheses, where appropriate).

Body weight	20–40 g
Respiratory rate	60–220/min
Tidal volume	0.09–0.23 mL
Oxygen use	1.63–2.17 mL/g/hr
Heart rate	325–780/min
Blood volume	70–80 mL/kg
Erythrocytes	7.0–12.5 × 10^6/mm^3 (7.0–12.5 × 10^{12}/L)
Hematocrit	39–49% (0.39–0.49 L/L)
Hemoglobin	10.2–16.6 g/dL (102–166 g/L)
Leukocytes	6–15 × 10^3/mm^3 (6–15 × 10^9/L)
Neutrophils	10–40%
Lymphocytes	55–95%
Eosinophils	0–4%
Monocytes	0.1–3.5%
Basophils	0–0.3%
Platelets	800–1,100 × 10^3/mm^3 (800–1,100 × 10^9/L)
Serum protein	3.5–7.2 g/dL (35–72 g/L)
Albumin	2.5–4.8 g/dL (25–48 g/L)
Globulin	0.6 g/dL (6 g/L)
Sodium	112–193 mEq/L (112–193 mmol/L)
Potassium	5.1–10.4 mEq/L (5.1–10.4 mmol/L)
Chloride	82–114 mEq/L (82–114 mmol/L)
Serum calcium	3.2–8.5 mg/dL (0.80–2.12 mmol/L)
Serum phosphate	2.3–9.2 mg/dL (0.74–2.97 mmol/L)
Serum glucose	62–175 mg/dL (33.4–9.7 mmol/L)
BUN	12–28 mg/dL (4.3–1.0 mmol/L)
Creatinine	0.3–1.0 mg/dL (27–88 umol/L)
Total bilirubin	0.1–0.9 mg/dL (2.0–15 umol/L)
Cholesterol	26–82 mg/dL (0.67–2.12 mmol/L)
AST	54–269 IU/L
ALT	26–77 IU/L
Alkaline phosphatase	45–222 IU/L

Urinalysis

Normal small rodent urine is variable in color, ranging from colorless to yellowish to light brown. Diet or antibiotics may cause porphyrin excretion, resulting in a reddish tinge. Small rodent urine SG values range from 1.003 to 1.060. Rats may concentrate urine to twice that measured in humans, and specific gravities of 1.020–1.050 are normal. The volume of urine produced is approximately 3.3–4.2 mL/100 g/day. Small rodent urine may be acidic or alkaline (pH 5–8.4). There is marked circadian fluctuation in small rodent urine pH, and the diet and protein source greatly influence the pH. Urine should always be collected at the same time of day for comparisons.

Urine protein levels may be significant in some small rodents. Mice produce approximately 0.5–2.5 mL of urine every 24 hours, and males are normally mildly proteinuric, with higher levels seen in sexually mature mice. Proteinuria is also normal in male rats due to sex-dependent tubular production of alpha-globulins, and urine protein levels can be as high as 30 mg/dL. Hamsters excrete an average of 9.7 mg protein in the urine weekly, approximately 10 times the urinary protein excretion rate of normal humans. Both normal hamsters and those with advanced renal disease may have proteinuria. Hamsters produce approximately 5–8 mL of urine per day, with calcium phosphate and carbonate crystals contributing to turbidity. Gerbils produce scant concentrated urine that may contain trace protein. Glomerulonephritis and amyloidosis are the most common causes of renal disease–associated proteinuria for small rodent species.

Glucose is not normally present in small rodent urine. Guinea pigs with diabetes mellitus may have urine glucose levels of 4.9–15.9 mmol/L. Guinea pigs with diabetes mellitus often present in a state of ketosis. Ketones are always interpreted to be abnormal when present in rodent urine and may be seen after prolonged anorexia or starvation or during pregnancy. Guinea pigs and chinchillas with dental disease and

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Table 3.10. Reference hematology and clinical chemistry values for rats (SI units are in parentheses, where appropriate).

Body weight	250–520 g
Respiratory rate	70–115/min
Tidal volume	0.6–2.0 mL
Oxygen use	0.68–1.10 mL/g/h
Heart rate	250–450/min
Blood volume	50–70 mL/kg
Blood pressure	84–134/60 mm Hg
Erythrocytes	$7–10 \times 10^6/mm^3$ ($7–10 \times 10^{12}$/L)
Hematocrit	36–48% (0.36–0.48 L/L)
Hemoglobin	11–18 g/dL (110–180 g/L)
Leukocytes	$6–17 \times 10^3/mm^3$ ($6–17 \times 10^9$/L)
Neutrophils	9–34%
Lymphocytes	65–85%
Eosinophils	0–6%
Monocytes	0–5%
Basophils	0–1.5%
Platelets	$500–1,300 \times 10^3/mm^3$ ($500–1,300 \times 10^9$/L)
Serum protein	5.6–7.6 g/dL (56–76 g/L)
Albumin	3.8–4.8 g/dL (38–48 g/L)
Globulin	1.8–3.0 g/dL (18–30 g/L)
Sodium	135–155 mEq/L (135–155 mmol/L)
Potassium	4–8 mEq/L (4–8 mmol/L)
Serum calcium	5.3–13.0 mg/dL (1.32–3.24 mmol/L)
Serum phosphate	5.3–8.3 mg/dL (1.71–2.68 mmol/L)
Serum glucose	50–135 mg/dL (2.8–7.5 mmol/L)
BUN	15–21 mg/dL (5.4–7.5 mmol/L)
Creatinine	0.2–0.8 mg/dL (18–71 umol/L)
Total bilirubin	0.20–0.55 mg/dL (3–9 umol/L)
Serum lipids	70–415 mg/dL (0.7–4.2 g/L)
Phospholipids	36–130 mg/dL (0.4–1.3 g/L)
Triglycerides	26–145 mg/dL (0.3–1.4 g/L)
Cholesterol	34–130 mg/dL (0.88–3.36 mmol/L)
ALT	16–89 IU/L
Alkaline phosphatase	16–125 IU/L

those with severely impacted ceca are common examples of patients with conditions inducing ketonuria.

Positive urine bilirubin is associated with destruction of heme from blood cells or muscle or disease of the biliary tree. Normal rodent urine has very few RBCs (0–3 cells/hpf). An increase may be seen with inflammation or damage to the urinary or reproductive system, such as occurs with infection, calculi, or neoplasia. Guinea pigs are particularly susceptible to urinary tract infections.

Urine from normal guinea pigs and chinchillas usually contains large amounts of light-colored sediment. Cloudy urine is usually caused by calciuria, which is normal to some extent in rodents. Amorphous calcium carbonate, struvite, and triple phosphate crystals are most common. Rodents being treated with sulfonamide drugs may have sulfur crystals. RBCs, WBCs, casts, and bacteria may be found in rodent urine and have the same interpretation and importance as in other mammals, that is, the presence of WBCs suggests infection, while casts suggest renal tubular disease.

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MEDICAL IMAGING

Diagnostic imaging of rabbits and rodents may facilitate diagnosis, assessment, and treatment of skeletal injury or disease, foreign body presence, gastrointestinal stasis, dental abnormalities, neoplasia, otitis media and externa, pregnancy, urolithiasis, and many other conditions. Radiography and ultrasonography are the most common and least expensive imaging techniques used; however, computed tomography (CT) and magnetic resonance imaging (MRI), are also used. Of these advanced imaging techniques, CT scans are particularly useful in rabbits, guinea pigs, and chinchillas. Intraoral dental radiographs may be needed for specific tooth radiography to provide increased detail. It is beyond the scope of this book to delve into specifics for each of the various imaging modalities. Interested readers are referred to the resources listed in the reference section.

Radiography

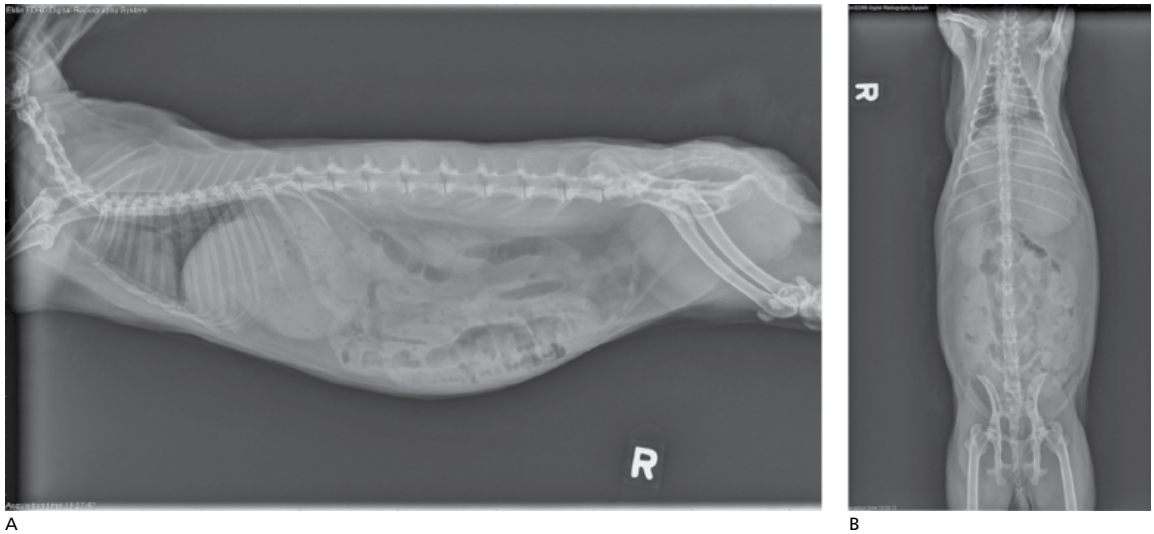
For rabbits and rodents, equipment should be capable of short exposure times (1/30–1/120 seconds), 5.0–7.5 milliampere second (mAs) exposures, and a range of 40–100 kilovoltage peak (kVp), adjustable in 1–2 kVp increments. A focal film distance of 90 cm is used commonly with detailed screen and film combinations.

Immobilization of patients is essential, as is a fast exposure time because of the rapid respiratory rate of rabbits and rodents. Radiolucent foam or tape is helpful for correct animal positioning. The fur should be clean and dry, as dirt or water may produce artifacts. Soft tissues in small mammals have a low density, so methods to enhance contrast are useful. High-resolution film screens, such as high-detail rare-earth intensifying screens with appropriate film, can be used to obtain diagnostic radiographs in small patients. Cassettes and screens designed for human extremities may be useful. Digital radiography is also recommended, whenever available.

Radiography of Rabbits

Skull, whole-body, thoracic, or abdominal radiography is often conducted in rabbits and is facilitated by sedation or anesthesia. Most patients may be adequately sedated using a combination of 1–1.5 mg/kg of midazolam and an opioid (typically butorphanol 0.5–1 mg/kg or buprenorphine 0.05 mg/kg). Ketamine 3–5 mg/kg may be added for animals requiring deeper sedation. In some cases, general anesthesia with isoflurane or sevoflurane or use of intravenous drugs such as propofol or alfaxalone may be required (at a lower dosage than for anesthetic induction, given the nonpainful procedure, see below).

Ventrodorsal and lateral views are standard for the spine, pelvis, thorax, and abdomen (Figure 3.15). Both right and left lateral views of the thorax should be taken to optimize information gained. The thoracic cavity of adult rabbits contains a large amount of fat, which may be superimposed over the cardiac apex and may mimic pleural fluid. Contrast in the



A B

FIGURE 3.15. Ventrodorsal (A) and lateral (B) survey radiographs of the thorax and abdomen of a normal rabbit.

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thoracic cavity can be increased by exposing the film at maximal inspiration, or using positive pressure inflation, if the animal is intubated. Pneumonia is commonly diagnosed in rabbits on radiographs. On radiographs, thymoma presents as a diffuse soft-tissue opacity in the cranial mediastinum with dorsal elevation of the trachea (see Figure 3.16 for a cross-sectional CT scan of a thymoma).

For skull radiographs, the dorsoventral view provides better evaluation of the tympanic bullae. In addition to the lateral view, rostrocaudal and oblique views may facilitate examination of other areas of interest, such as the teeth, orbits, or nasal cavity.

Objective evaluation of malocclusion in most rabbits can be made by using specific anatomical reference lines, particularly on lateral views of the head. In rabbits with normal dentition the maxillary cheek teeth apices should not protrude above a line drawn from the tip of the nasal bone to the occipital protuberance (see upper red dotted line in Figure 3.17). The normal dental plane is represented by another line drawn from the tip of the hard palate to 1/3 of the height of the tympanic bullae. The mandibular cheek teeth apices should not elongate below the mandibular bone margin. Reference lines outlining the hard palate and mandibular diastema should converge in normal occlusion. The palatal angle, which is the angle between the plane of the base of the skull and the palatal plane, should be measured prior to using this method. If the angle is greater than 18.8° the maxillary cheek teeth will protrude beyond the occlusal reference line, which could lead to a misdiagnosis of malocclusion in these cases. A skull radiograph from a rabbit with malocclusion is seen in Figure 3.18.

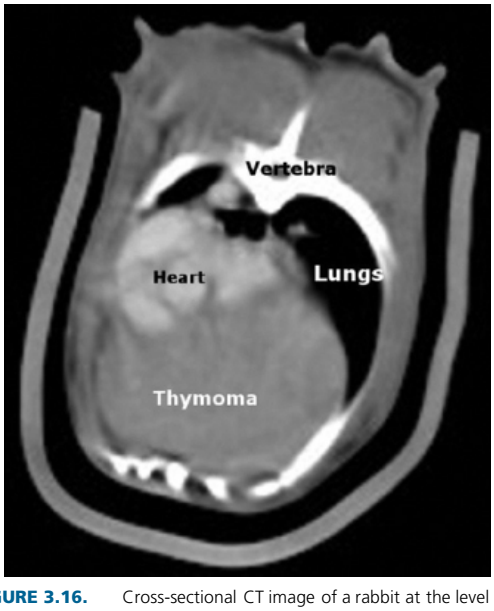


FIGURE 3.16. Cross-sectional CT image of a rabbit at the level of the cranial thorax showing a thymoma, which displaces the heart.

Skull radiographs generally are not sensitive for diagnosing otitis media, and CT scan is recommended for this condition (Figure 3.19). Readers are invited to consult specific references for more details on interpretation of normal and pathologic skull radiographs.

Dorsopalmar and dorsoplantar views are used for the front and rear legs, respectively, along with mediolateral views for the appendicular skeleton.

Variations in both normal and abnormal rabbits make interpretation of abdominal radiographs challenging. Large fatty

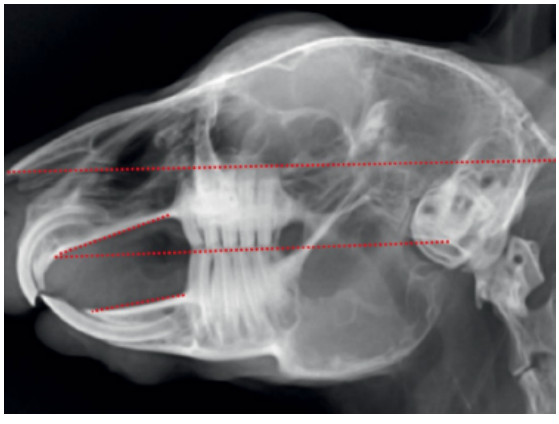


FIGURE 3.17. Lateral radiographic view of the skull of a normal rabbit with reference lines used to assess the teeth. The top long dotted red line goes from the nasal bone to the occipital bone, and the reserve crowns for the maxillary cheek teeth should not go beyond this line. The middle long dotted line goes from the hard palate to the lower 1/3 of the tympanic bulla and should align with a normal occlusion plane. The short dotted lines outline the hard palate and mandibular interdental space and should converge rostrally in normal occlusion.



FIGURE 3.18. Moderate-to-severe dental disease in a rabbit: Note the incisor and cheek teeth malocclusion. The reserve and clinical crowns of both the incisors and cheek teeth are elongated, the mandibular bone is remodeled and the dental plane is abnormal.

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livers and gastrointestinal gas accumulation are common findings, and the cecum may be large and fluid-filled. Rabbits excrete large amounts of calcium via the kidneys, and these calcium salts are often visible on radiographs in the urinary bladder as a normal finding. Nephroliths and cystic calculi are commonly diagnosed on radiographs. Spondylosis lesions are also commonly seen in older rabbits. In rabbits presented for gastric stasis, the following lesions may be observed on radiographs: an enlarged stomach, and gas in the stomach, intestines, and cecum (Figure 3.20). Multiple calcified masses in the abdomen are commonly seen with metastatic uterine adenocarcinoma.



FIGURE 3.19. Cross-sectional CT view of a rabbit at the level of the osseous bulla. The left osseous bulla is filled with soft-tissue materials suggestive of otitis media.

Radiography of Rodents

Similar procedures to rabbits may be conducted to obtain radiographs on large hystricomorph rodents (i.e., guinea pigs and chinchillas). Small myomorph rodents (hamsters, gerbils, mice, and rats) are typically briefly anesthetized with isoflurane or sevoflurane alone. Immobilization using a low-dose mixture of ketamine with dexmedetomidine or acepromazine may be used, but are of lower safety in sick or otherwise compromised individuals without additional oxygen supplementation.

A sedated or anesthetized rodent can be placed directly on the cassette or can be positioned using radiolucent foam or tape applied circumferentially to a limb and then to the cassette or table for extension. The dorsoventral (sternum down) position is preferred over ventrodorsal, and tape can also be used to flatten the neck, limbs, and tail. Other views are taken as for rabbits. For skull imaging, additional views can be obtained in the guinea pig and chinchilla to isolate either the mandibular cheek teeth or the maxillary cheek teeth (Figure 3.21). For an isolated mandibular view, the patient is positioned in sternal recumbency, and the mouth is open wide using gauze or tape with the head in extension in such a manner that the x-ray beam is centered on the intermandibular area. For an isolated maxillary view, the patient is positioned in dorsal recumbency and the head is extended and orientated caudodorsally placing padding under the neck to accentuate neck extension and pulling on the top incisors with gauze or tape. Reference lines to assess dentition have been determined for chinchillas and guinea pigs as well but are not as straightforward to determine than in rabbits.

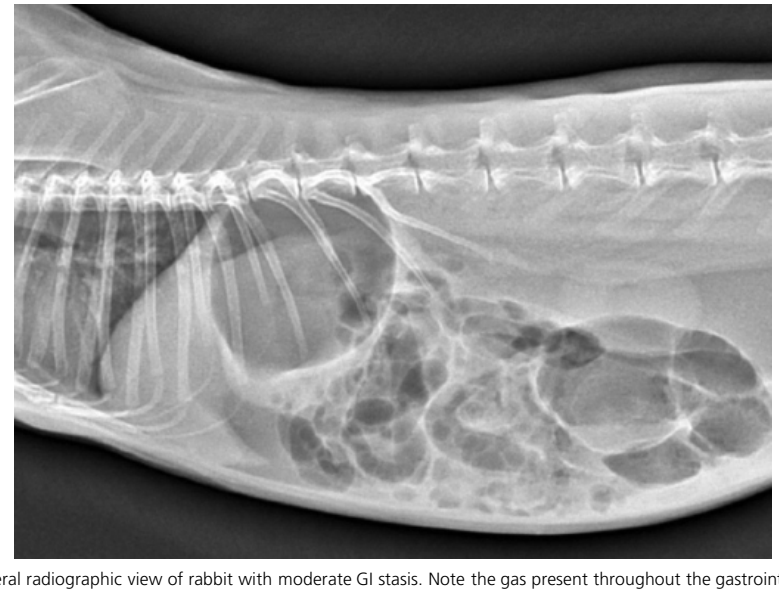


FIGURE 3.20. Lateral radiographic view of rabbit with moderate GI stasis. Note the gas present throughout the gastrointestinal tract.

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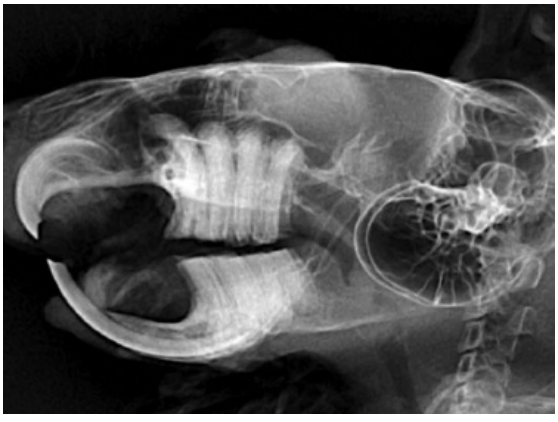


FIGURE 3.21. Radiograph demonstrating severe dental disease in a chinchilla. The reserve crowns of the maxillary cheek teeth are very elongated, the dental plane is abnormal, and the intraoral clinical crown elongation displaces the mandible caudally.

The abdomen is large compared with the thorax, and the large gastrointestinal tract shows little contrast but usually contains ample gas. In guinea pigs and chinchillas, the cecum takes up much of the abdomen, whereas the abdominal anatomy of hamsters, gerbils, mice, and rats is more similar to that of the dog or cat. All small rodents have an os penis (baculum), which should not be confused with a urolith.

Contrast Radiography

Contrast radiography by various methods allows clearer evaluation of the gastrointestinal tract, urinary bladder, and other organs. In rodents, soft tissues of the upper respiratory and upper digestive tracts have low density, and on radiographs, these tissues are poorly defined. For assessment of the stomach, pneumogastrography can be used, which involves introducing 5 mL air/kg body weight into the stomach through a tube, to evaluate the position or identify extraluminal masses. Positive contrast studies can be performed with appropriate radioopaque material (e.g., barium, iohexal) given orally at 3–20 mL/kg body weight to investigate stomach position, shape, and emptying time. Contrast studies should be performed with the stomach empty, if possible; however, rabbit stomachs are never completely empty. In rodents, emptying times vary between species, but in general, gastric emptying begins within 30 minutes of feeding and is complete by 3 hours. In rabbits, contrast reaches the cecum in approximately 4 hours and is retained there for prolonged periods. Contrast may stay in the stomach for days. Colonic radiography involves retrograde infusion of a contrast medium into the distal colon with a catheter (12–14 Fr).

Both negative (i.e., via installation of air or carbon dioxide) and positive (i.e., via installation of radioopaque material, such as a sterile iodine-based solution) contrast can be used for retrograde urinary cystography, provided a sterile urinary catheter can be placed. An intravenous pyelogram may be possible if catheterization of the cephalic, lateral saphenous, or tail vein can be accomplished for injection of contrast media. Excretory urography is useful for evaluation of size, shape, position, and internal structure of the kidneys, ureters, and urinary bladder.

Contrast radiography of the nasolacrimal duct (dacryocystography) in rabbits can be performed by cannulating the duct and flushing with radioopaque material.

Ultrasonography

Ultrasonography is a valuable adjunct to radiography and can be used to further investigate radiographic findings or as directed by the history and clinical findings. Point-of-care ultrasound is also increasingly used for routine imaging during the physical examination of patients presented as emergencies. An abdominal ultrasound examination is recommended for all rabbits presenting with gastrointestinal stasis (Figure 3.22). Ultrasonography allows differentiation of fluid from soft tissues and also permits inspection of the organ parenchyma, and is particularly useful for evaluating the urinary bladder, heart, uterus, liver, spleen, kidneys, and ovaries (Figure 3.23). The ultrasound beam is obstructed by gas, and because of this ultrasonography of the abdomen of small herbivores may be less helpful than for dogs and cats. The dynamic nature of ultrasonography allows for assessment of gastrointestinal motility and blood flow, using Doppler mode. Ultrasound-guided fine-needle aspirates and biopsies can also be performed, as needed. Echocardiography may be used to assess cardiac function, valvular insufficiency, and to take measurements. Reference values have been published for rabbits and most commonly seen rodents. Ultrasonography is also useful for investigating middle-ear disease in rabbits. Ultrasound examination of the tympanic bullae can be performed to detect fluid accumulation using standard



FIGURE 3.22. Intra-abdominal abscess in a rabbit seen on abdominal ultrasound examination.

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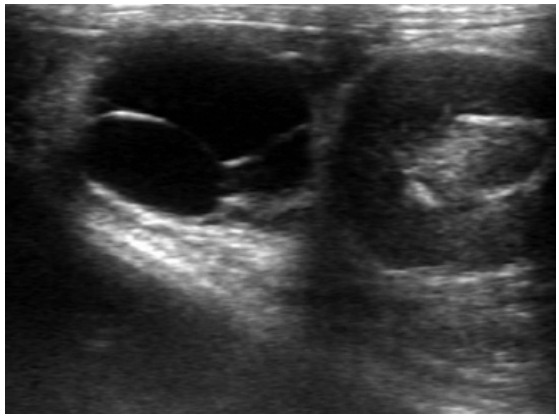


FIGURE 3.23. Ovarian cysts in a guinea pig seen on abdominal ultrasound examination.

equipment and is more accurate than radiography. Ultrasound may also be used to assess the retroorbital area, as abscesses and other masses in this area are common. Chest ultrasonography is a convenient way to obtain aspirates from a thymoma-like mass and confirm the diagnosis in a minimally invasive manner.

For small mammals, a minimum requirement is a high-definition transducer with a footprint of less than 2 cm. Sedation or anesthesia is required for most species, and body hair must be clipped to exclude air between the transducer and the skin. Acoustic coupling gel should be applied liberally to both the transducer and the skin. Hypothermia is a concern due to hair loss, wetting of the skin surface, and general anesthesia, and must be guarded against, particularly in very small animals.

Computed Tomography Scanning

CT is very useful in rabbit clinical practice. Images are acquired in cross-sections but can be reconstructed in any plane as well as in 3D. The sensitivity of CT images to diagnose most disorders in rabbits is far superior to conventional radiographs. CT scan of the skull is steadily replacing skull radiographs in exotic specialty practices to assess dentition and is indispensable in the diagnosis of otitis media/interna as radiographs have low sensitivity. Overall, CT scan is particularly useful for diagnosing and characterizing dental disorders, rhinitis, retrobulbar conditions, thymoma, and otitis. Cone-beam CT (CBCT), while less commonly used in rabbits, has a higher resolution for dental imaging, but generally has poor soft-tissue contrast when compared to multi-slice CT scan.

Sedation or inhalant anesthesia may be used. A sedation protocol in rabbits of midazolam 1.5 mg/kg IM combined with an opioid usually works well. Ketamine 3–5 mg/kg IM or small 1–2 mg/kg IV boluses of propofol may be given in more anxious animals. General anesthesia with isoflurane is also an alternative to deep sedation. An intravenous catheter must be placed for iodinated contrast administration (same dosage as dogs and cats). Contrast enhancement has proven to be particularly useful to highlight inflammatory and neoplastic lesions and highlight abscess capsules.

Magnetic Resonance Imaging

MRI uses a magnetic field and various radiofrequency pulses and gradients to generate tissue images (MRI sequences). Spatial resolution and soft tissue contrast are greater with this technique than with CT, and the tissues can be imaged in any plane. The animal must be completely immobilized by general anesthesia, as any movement will blur the image as image acquisition is typically slower than for CT scanning. Anesthesia must be performed and monitored using MRI-compatible equipment. In addition, the scanning time may be long and the MRI rooms are usually cold, increasing the risk for small patients. MRI is very useful for musculoskeletal, articular, and cerebral imaging, and for longitudinal studies of soft tissue, as well as for viewing inflammation and neoplasia. MRI is primarily used in research settings and for cerebral and spinal imaging of companion rabbits and larger rodents.

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OPHTHALMOLOGY

Ocular disease of rabbits and rodents is evidenced by changes similar to those as seen in other companion animals. Common presenting signs include epiphora, blepharospasm, exophthalmos, and lens, or corneal opacities. Dental disease with reserve crown elongations, in particular of the maxillary incisors and the first maxillary premolars, may lead to obstruction of the nasolacrimal ducts and subsequent dacryocystitis and epiphora. Reserve crown elongations and retrobulbar apical infections of the maxillary molars may lead to exophthalmos and exposure keratitis, which is more common in rabbits than in rodents. Ophthalmic diseases specific to rabbits include *E. cuniculi*-induced phacoclastic uveitis and aberrant conjunctival overgrowth. Specific infectious diseases target ophthalmic tissues in rodents as well such as chlamydial infection in guinea pigs or sialodacryoadenitis coronavirus in rats.

Orbital lesions may result from infections, nutritional deficiencies, injury, congenital malformations, husbandry practices, and as a sequela to retroorbital bleeding (a historic practice in some research settings). The lateral placement and bulbous nature of the eyes of rabbits and rodents, which is typical of prey species, predisposes them to traumatic or iatrogenic ulcers, especially during sedation and anesthesia, when they may be placed in lateral recumbency. Rabbits' eyes are also normally buphthalmic, which further predisposes them to iatrogenic corneal ulcers under anesthesia.

Vision assessment in these animals can be difficult because many are nocturnal and depend on olfactory and tactile cues. Most are housed in familiar quarters and are rarely exercised outside the home enclosure or venture into novel areas. In addition, the small size of the eye in rodents and difficulty in restraint of the head can hinder examination, for those without practice. Direct or indirect ophthalmic exams are conducted routinely in conscious mice and rats in research settings.

Equipment and Methods

Typical equipment needed for ophthalmic examination optimally includes an ophthalmoscope, a rebound or applanation tonometer, fluorescein stain strips, and a method for measuring tear production. A handheld condensing lens and bright light source can also be used for indirect ophthalmic examination, as for other veterinary species. Schirmer tear test (STT) strips can be used in rabbits and rodents if their eyes are large enough. The thread used in the phenol red tear test is smaller and requires less tear volume and a shorter testing time of 15 seconds, which may be more appropriate for animals with smaller eyes. The relatively newer endodontic paper point tear test (EPPTT) makes use of small, standardized pieces of highly absorbent, conically shaped material used in dentistry for drying root canals and allowing disinfectants to be carried into small areas. These devices are placed into the fornix for 1 minute after which the wet portion is measured in mm with digital calipers. These paper points have shown promise for measuring tear production in a variety of species as they are easy to use, especially in very small eyes, the results are reliable, and they cause very little conjunctival irritation. A slit lamp biomicroscope and an indirect ophthalmoscope are also useful pieces of equipment but are usually only found in research settings or owned by veterinary ophthalmologists due to their expense.

The ophthalmic examination is very similar to other companion animals keeping species-specific differences in mind. A systematic approach should be used, starting with tests of vision, examination of eyelids, surrounding skin (including nares) and visible eye structures (conjunctiva, sclera, and cornea), and comparison of the two globes. Rabbits and rodents rarely have a menace response, but other ocular reflexes are similar to other species. Assessment of tear production and measurement of intra-ocular pressure should be performed via the method most appropriate for the species. Topical anesthetics should be used sparingly in very small rodents to prevent systemic toxicity, but they are usually necessary for manipulations of the eye and adnexa. The lids can be retracted to examine the conjunctival sac, and in rabbits, the single large nasolacrimal punctum, which lies ventrally at the fornix. Examination of the cornea, anterior chamber, lens, and vitreous should be performed, if possible, with a slit lamp. The pupils can be dilated with a mydriatic such as 1% tropicamide for examination of the fundus. Animals with pigmented irises (usually brown) may bind the mydriatic agent to uveal melanin. In these animals, a drop of 1% atropine combined with one drop of 10% phenylephrine can be given three to four times over a 15-minute period. Fundic examination is conducted using direct or indirect ophthalmoscopy with a 30–40 diopter lens. Rabbits may have plasma atropine esterase, which may preclude pupillary dilation with alkaloid mydriatics.

Other useful procedures include fluorescein dye staining to evaluate the cornea and patency of the nasolacrimal system,

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bacterial culture, and conjunctival scrapings. With epiphora and exophthalmos, additional diagnostics should also be performed to assess the teeth and the possibility of a thoracic mass, especially in rabbits.

Rabbits and most rodents have a large retrobulbar venous plexus that renders enucleation quite challenging in these species.

Rabbits

The rabbit eyeball has a large cornea, large rounded lens, and poorly developed ciliary body. Eyelids separate completely at approximately 10 days after birth. Rabbits blink an average of only 10–12 times an hour compared to 1,000 times/h in humans. The fundus is merangiotic (partially vascularized) with intravitreal vessels at a level nasal and temporal to the optic disc. The myelinated optic disc is depressed centrally and lies above the horizontal midline, which necessitates looking "up" into the rabbit's eye to see it. The superior rectus muscle is normally visible through the superior bulbar conjunctiva. The orbit contains four glands: lacrimal, intraorbital, Harderian, and gland of the nictitating membrane. The nictitating membrane (third eyelid) is functional and extends from the medial canthus. Flushing of the nasolacrimal duct is not difficult and is described in the section "Other Special Techniques."

Normal STT values for the rabbit range from ~0 mm/min to 11 mm/min, depending on the study. Low values can be obtained in healthy rabbits, and the significance of this test has been questioned. Values of 21 mm/15 seconds (range 15–27 mm/15 s) have been reported for the phenol red thread tear test (PRTT) and measurements of ~12 to 16 mm/min can be found for the endodontic paper point tear test (EPPTT).

Normal intraocular pressure (IOP) depends on the device used, with values of ~9–10 mmHg reported with rebound tonometry (Tonovet®) and ~12–17 mmHg reported with applanation tonometry (Tono-Pen Avia®), depending on the study. The IOP was found to be higher early in the day compared to later, regardless of the device used.

Common ocular problems in rabbits include epiphora, conjunctivitis or blepharoconjunctivitis (Figure 3.24), corneal ulcers, cataracts, glaucoma, uveitis, exophthalmos due to orbital abscess (Figure 3.25), orbital neoplasm, or thymoma, prolapse of the third eyelid ("cherry eye"), and aberrant conjunctival overgrowth (pseudopterygium). Other disorders, such as congenital abnormalities, entropion, corneal opacities, keratoconjunctivitis sicca, and ocular colobomas, have also been reported.

Epiphora is seen with either excessive tear production from ocular irritation or infection, or inadequate tear drainage due to an obstructed nasolacrimal duct. The condition manifests as crusting and matting of the hair at the medial canthus. Dystichiasis (abnormally positioned eyelashes) and trichiasis (ingrown eyelashes) have been reported in rabbits and are treated as for dogs. Nasolacrimal duct obstruction is a common sequela to chronic rhinitis or dacryocystitis caused by



FIGURE 3.24. Conjunctivitis in a rabbit with prolapse of the nictitating membrane.

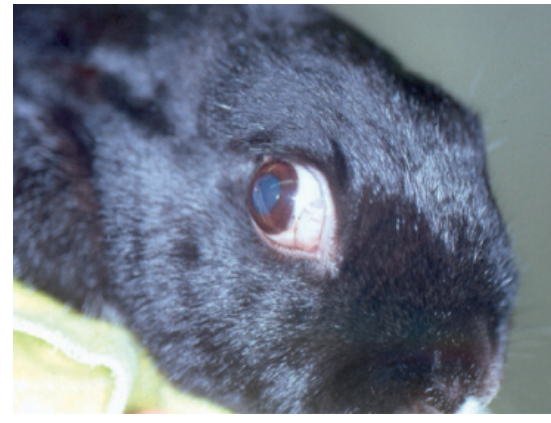


FIGURE 3.25. Exophthalmos in a pet rabbit secondary to a retrobulbar abscess.

Pasteurella multocida and also commonly occurs secondary to dental disease due to elongation of the reserve crowns of the maxillary incisors and first premolars. Patency of the duct can be determined by instilling fluorescein dye in the conjunctival sac and watching for drainage at the respective nare. Flushing of the duct may relieve the obstruction, but care must be taken not to apply too much pressure as rupture of the duct and subsequent abscess formation may occur (Figure 3.26). If the obstruction cannot be relieved by flushing, twice daily warm compresses and massage over the rostrum for several days may help. Addressing any dental issues is also important.

A variety of bacteria have been reported to cause conjunctivitis in rabbits including *P. multocida, Staphylococcus aureus, Pseudomonas* spp., and *Chlamydophila* spp. Depending on reports, either *P. multocida* or *S. aureus* are found to be the most prevalent bacteria isolated. The bacteria may be present in the conjunctival sac or extend from the nasal cavity through

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FIGURE 3.26. Epiphora and facial swelling secondary to rupture of the nasolacrimal duct in a pet rabbit.

the nasolacrimal duct or invade the duct through a periapical infection of the maxillary teeth. Purulent material can often be expressed into the conjunctival sac from the duct by applying digital pressure to the skin ventral to the medial canthus of the eye. *P. multocida* infections can also result in orbital cellulitis, uveitis, and conjunctivitis. Ammonia accumulation in the environment due to poor husbandry practices or inadequate ventilation may also induce conjunctivitis. Other causes of conjunctivitis, blepharitis, and epiphora include trauma, eyelid malformations, dystichiasis, trichiasis, and myxomatosis. Treatment usually includes topical antibiotic drops and addressing the risk factors.

Blepharitis may be seen in cases of rabbit syphilis, caused by *Treponema paraluiscuniculi*. Spirochetes may be seen on scrapings of the infected area. Myxomatosis may also cause blepharitis. Protracted dacryocystitis and dental disease may also lead to periocular dermatitis and blepharitis.

Corneal ulcers are also common. The lateral placement of the eyes and the large corneal area predisposes them to trauma. Ulcers may also occur due to decreased tear production (facial nerve paralysis commonly seen in otitis media), and exposure keratitis due to acquired buphthalmia (glaucoma), exophthalmos (thymoma, retrobulbar disease), or anesthesia. The treatment is similar to that in other companion animals and includes artificial tear products, autologous serum, and topical antibiotic drops, depending on the extent and severity. Indolent ulcers may also be diagnosed, in which case corneal debridement and a grid keratotomy may be indicated. Temporary tarsorrhaphy may also help in rabbits with facial nerve paralysis. Rabbits that don't close their eyes during anesthesia should have a temporary tarsorrhaphy performed prior to long procedures as corneal ulceration is extremely common in this situation. For descemetocele and perforated ulcers, enucleation or conjunctival grafts are recommended. Other causes of corneal opacities include inherited corneal dystrophy (in Dutch rabbits), dietary and inherited lipid keratopathy, and calcific keratopathy. Watanabe Heritable Hyperlipidemic (WHHL) rabbits exhibit ocular lesions consistent with lipid keratopathy. The condition is characterized by accumulation of lipid-laden macrophages in the cornea, iris, and ciliary body.

Congenital buphthalmia (enlargement of the eye from excessive intraocular fluid accumulation), often with secondary glaucoma, occurs in New Zealand white (NZW) and some cross bred rabbits. In NZW rabbits, it is an inherited autosomal recessive trait with incomplete penetrance and is characterized by uni- or bilateral buphthalmia that may progress to include corneal edema and blindness. The onset may be as early as 1 month of age, but more typically it occurs at 3–6 months. Treatment of congenital glaucoma in New Zealand white rabbits is unrewarding as the effects of topical miotic and beta-blocking drugs are usually not sufficient to preserve vision.

In companion rabbits, glaucoma can be hereditary or secondary to other ocular conditions such as cataracts, uveitis, or other ocular disease (Figure 3.27). Clinical signs may include loss of vision, buphthalmia, conjunctivitis, blepharitis, hyphema, corneal edema, elevated IOP, optic nerve head cupping, mydriasis, and cataract formation. Treatment with newer carbonic anhydrase inhibitors such as dorzolamide and brinzolamide or prostaglandin analogues such as latanoprost may be effective in reducing IOP. Surgical therapies include cyclocryotherapy and diode laser cycloablation for potentially sighted eyes, and evisceration with prosthesis implantation or enucleation for blind eyes. Intraoperative hemorrhage from the orbital venous sinus is a possible complication of enucleation but is often self-limiting before serious consequences occur.

In one retrospective study of 11 rabbits aged 8 months–12 years of age diagnosed with glaucoma, mean IOP was 39 mmHg (measured by either applanation or rebound tonometry) with a range of 26–55 mmHg (cut-off for inclusion was 25 mmHg in this study). Topical treatment was successful in two rabbits (18%), two rabbits underwent unilateral enucleation, and seven rabbits (64%) did not respond to topical medications, which



FIGURE 3.27. Rabbit with glaucoma. Courtesy of Calgary Avian & Exotic Pet Clinic.

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included dorzolamide, latanoprost or 0.5% timolol alone or in various combinations. Use of intravitreal gentamicin as an alternative to anesthesia and enucleation in high-risk patients, or for owners who cannot afford eye removal may be an option in some cases. Intravitreal gentamicin has been shown to decrease IOP, but other ocular complications can occur, and the systemic absorption of gentamicin from the eye, and subsequent potential for renal toxicity is not fully known.

Uveitis is associated with ocular trauma, ulcerative keratitis, systemic infection, and spontaneous lens rupture (phacoclastic uveitis) sometimes attributable to *E. cuniculi* infection. Treatment involves use of topical anti-inflammatory and antimicrobial agents, similar to those for other species. Severe infections and phacoclastic uveitis often require enucleation. Unilateral exophthalmos in rabbits is most often caused by retro-orbital abscesses associated with dental disease. In advanced cases with exposure keratitis or panophthalmitis, enucleation, tooth extraction, and draining of the orbit may be successful if hemorrhage is appropriately controlled. In cases where the eye is still intact, it may be possible to spare the globe by using a periocular approach. Marsupialization of the abscess cavity, packing with antibiotic impregnated polymethylmethacrylate beads, or packing with antimicrobial-impregnated gauze are some treatment options. A surgical approach just under the globe and above the zygomatic arch is usually effective. In some cases, a zygomatic arch resection may be necessary to better access the abscess. Other reported causes of unilateral exophthalmos include presence of *Taenia serialis* coenurus, orbital neoplasia, cellulitis, retrobulbar fat prolapse, and salivary mucocele. Bilateral exophthalmos has been associated with mediastinal masses such as thymoma or lymphoma, and as a consequence of chronic external jugular catheter placement. Temporary bilateral exophthalmos also occurs with stress and restraint.

Aberrant conjunctival overgrowth (pseudopterygium) is an uncommon, idiopathic condition, unique to rabbits and characterized by bilaterally symmetrical annular conjunctival overgrowth of the cornea. Surgical excision of the conjunctival tissue is usually ineffective as conjunctiva tends to regrow. The recommended technique involves centrifugal incisions of the overgrowing conjunctiva to the limbus followed by eversion and transpalpebral fixation. Recurrences may still occur.

Prolapse of the gland of the third eyelid may be uni- or bilateral in rabbits. The cause is unknown, and surgical correction is usually successful in uncomplicated cases.

Cataract is also frequently seen in rabbits. Cataracts in young rabbits are generally attributed to *E. cuniculi* infection transmitted in utero. Spontaneous juvenile cataracts have been reported to occur with an incidence of 5.7% in New Zealand white rabbits, which is consistent with an autosomal recessive mode of transmission. Secondary cataract formation can be seen after chronic uveitis. Diabetic rabbits may develop osmotic cataracts similar to those found in dogs. Treatment relies on the control of the associated uveitis or cataract surgery. If a cataract surgery is performed, an electroretinogram is recommended to ensure the retina is visual.

Congenital abnormalities of the rabbit eye are rare. Entropion and ectropion have been reported and can be surgically corrected. Cyclopia, persistent hyperplastic primary vitreous, lens coloboma, and optic nerve coloboma have been reported.

Guinea Pigs

Guinea pigs have a paurangiotic (nearly avascular) fundus, with only a few capillary loops near the central optic disc. Guinea pigs are born precocious, and the eyelids are separated at birth. The nictitating membrane is rudimentary and consists of a fold of conjunctiva near the medial canthus. An upper and lower lacrimal punctum is present. Six glands contribute to tear production in guinea pigs, including the Meibomian glands, the intraorbital gland, the extraorbital gland, the Harderian gland, and two sebaceous glands. Guinea pigs blink very infrequently, averaging two to five times over 20 minutes at rest and 0–17 times over 10 minutes when handled.

Reported SST measurements of tear production in guinea pigs vary widely, depending on the study, ranging from ~0.36 mm/min to 12 mm/min. Tear evaluation using the PRTT can vary from ~10 mm to 32 mm/15 s. Using the EPPTT, values of ~7–10 mm/min have been reported.

Intraocular pressure using rebound tonometry ranges from ~5 mmHg to 9 mmHg. Applanation tonometry yields values of 8–28 mmHg.

Ocular disorders include blepharitis, conjunctivitis, "pea eye" (an inferior conjunctival mass), scleral and corneal mineralization, cataract, and panophthalmitis. Blepharitis may be caused by dermatophytes, especially in young animals. Conjunctivitis can be seen with infectious agents, such as *Chlamydophila caviae*, streptocci, *Micrococcus* spp, *S. aureus*, *P. multocida, Bordetella bronchiseptica, Proteus* spp, and pneumococci, but may also be seen secondary to ascorbic acid deficiency. *C. caviae* infection can be enzootic and transmission is primarily venereal, with neonates infected at birth. Lesions usually resolve in approximately 1 month and treatment is considered unnecessary, unless the animal is severely affected. Conjunctival scrapings may yield typical intracytoplasmic chlamydial inclusions with Gimenez or Macchiavello's stain. Conjunctival cytology characteristic of bacterial conjunctivitis typically consists of numerous heterophils with or without intracellular bacteria. Lymphosarcoma with conjunctival involvement has been reported.

"Pea eye" describes a condition in which a subconjunctival nodule protrudes from the conjunctival sac in one or both eyes (Figure 3.28). The enlargement is thought to be a portion of the lacrimal or zygomatic glands. Concurrent ventral ectropion may result, but treatment is usually unnecessary. Corneal and scleral calcification occurs in guinea pigs with or without simultaneous mineralization elsewhere. Cortical

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FIGURE 3.28. "Pea eye" in a guinea pig. Courtesy of Calgary Avian & Exotic Pet Clinic.

cataracts are not uncommon and are suspected to be genetic in origin. In a study of 1,000 apparently healthy guinea pigs, 45% had some ocular abnormality, mostly involving the lens, with 17% having cataract and 21% with subclinical lens pathology.

Panopthalmitis may occur secondary to *Streptococcus zooepidemicus* abscess formation and bacteremia.

Chinchillas

Chinchillas have an anangiotic retina (without blood vessels), a rudimentary third eyelid, and a vertical pupillary slit. Like guinea pigs, they are precocial and born with the eyelids already separated. Chinchillas possess Meibomian glands, a Harderian gland, and a lacrimal gland. Two lacrimal puncta are present. Blink frequency has been recorded as ~3 times/10 min. The STT has been reported as not reliable and low, with values of ~1–2 mm/min. Tear production as measured by the PRTT ranges between ~8–22 mm/15 s and by the EPPTT yields values of ~8 mm/min. Both rebound and applanation tonometry can be used to measure IOP in chinchillas, with values of ~2–10 mmHg reported for the former and ~ 18 mmHg for the latter.

Asteroid hyalosis and cataracts have been reported in older animals. Exophthalmos caused by orbital *Taenia* spp. coenurus and retrobulbar odontogenic abscesses has been reported in the chinchilla.

Hamsters and Gerbils

Small rodents have a holangiotic retina (central blood supply) with radial vessels and a centrally located optic disc. Light entering the eye is focused on the entire retina. Syrian hamster eyelid separation occurs at approximately 15 days and Chinese hamster eyelid separation occurs between 10 and 14 days. In Syrian hamsters, the eye blink frequency ranges from ~1–2 blinks/min. PRTT values of 3–11 mm/15 s and EPPTT values of ~2–7 mm/min have been reported. The IOP using rebound tonometry ranges from 2 mmHg to 8 mmHg. The shallow anterior chamber of the eye loses fluid rapidly with continuous eyelid opening such as during anesthesia. This can lead to temporary corneal and lens opacities until sufficient lubrication and blinking are reestablished.

Mongolian gerbil eyelid separation occurs 16–22 days after birth. Gerbils have a well-developed third eyelid supported by a piece of cartilage. Meibomian glands, a Harderian gland, and a lacrimal gland are present.

Similar ocular disorders have been reported for hamsters and gerbils as for other rodent species (Figure 3.29). Keratoconjunctivitis may be caused by infections, environmental dryness, or cagemate trauma. Prolapse of the globe is not uncommon in hamsters due to the shallow orbits. Because of their nocturnal nature, the globe is usually severely damaged by the time the problem is detected, and enucleation is often necessary. Some laboratory strains of Chinese hamsters spontaneously develop diabetes mellitus and secondary cataracts. Facial dermatitis is common in gerbils and is characterized by erythema, alopecia, and crusting of the external nares, muzzle, and periocular areas. The cause is unclear but a multifactorial etiology is suspected, including reduced grooming and inappropriate cage bedding.

Mice and Rats

Mice and rats also have a holangiotic retina. Rats have three tear-producing glands, the intraorbital, exorbital, and Harderian, which is associated with the third eyelid. Measurement of tear production using endodontic paper points in rats and mice is safe, reliable, and easier to perform than the phenol red tear test, as, unlike the phenol red thread, the firmer paper points do not require the use of forceps for placement. EPPTT values in mice and rats have been measured as ~4–5 mm/min and 4–8 mm/min, respectively.

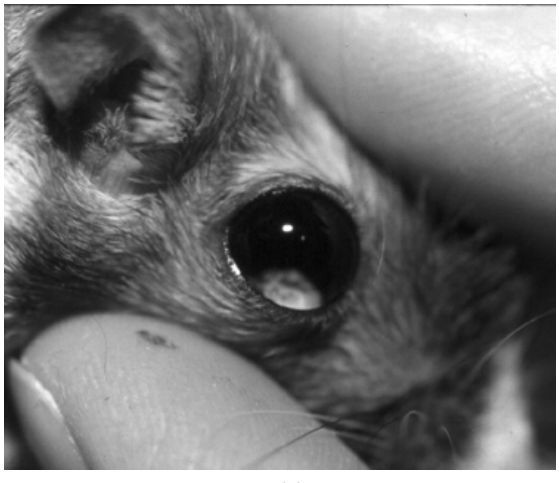


FIGURE 3.29. Cataract in a gerbil eye.

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In rats, porphyrin-pigmented tears are normally produced, predominantly by the Harderian gland, and production is controlled by parasympathetic innervation. Factors that increase parasympathetic activation increase the level of Harderian gland porphyrin production and may result in chromodacryorrhea or red tear production. Physiological stress and diseases such as mycoplasmosis and sialodacryoadenitis are important causes of chromodacryorrhea.

The most common cause of conjunctivitis in companion rats and mice is mycoplasmosis. Purulent conjunctivitis has been associated with *Pasteurella* spp. in rats with an underlying mycoplasma infection. Poor ventilation and improper handling can also contribute to conjunctivitis.

In rats, sialodacryoadenitis caused by coronaviral infection leads to conjunctivitis and periorbital swelling, followed by lymphadenopathy and salivary gland swelling. The disease is highly contagious but usually self-limiting. Permanent damage to the lacrimal gland and reduced tear production may occur post infection. In addition, keratitis and conjunctivitis may lead to chromodacryorrhea and self-mutilation. Diagnosis is made by classic pathognomonic signs, detection of coronavirus antigen, or serological testing of the animals.

Keratitis, corneal ulceration, and hypopyon have been reported in rats and mice following injectable anesthesia with ketamine/xylazine combinations, even when intraoperative eye lubricants are used (Figure 3.30). The cornea and subcorneal structures receive oxygenation from the anterior chamber. Injectable anesthetic agents may induce profound hypoxemia as well as hypotension, and it is hypothesized that this may result in corneal damage during anesthesia and prolonged postoperative recumbency. Animals undergoing injectable anesthesia should be supplemented with oxygen by face mask and reversed with specific pharmacologic agents, whenever possible, to minimize the risk of corneal hypoxia and injury.

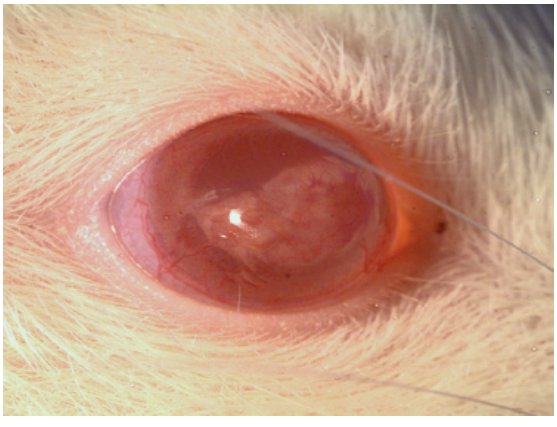


FIGURE 3.30. Corneal scarring and neovascularization in a rat as a sequela to ulceration. Reproduced with permission from American Association for Laboratory Animal Science.

Spontaneous microphthalmia occurs incidentally in rats, notably in the F344 rat, as well as various strains of mice, such as the C57BL/6. Defective tear drainage and microbial contamination of the conjunctival sacs can result.

Retinal degeneration can be seen in rats and mice under constant illumination and has also been reported as a spontaneous defect in albino rats and a number of different mouse strains, such as black Swiss and NIH Swiss mice. Strain-specific ophthalmic characteristics may have important implications for animal performance during behavioral tests that have a visual component. It is important to ensure that animals that perform poorly on these tests are sighted.

Subepithelial mineralization of the cornea, apparent as focal corneal opacities, has been reported in both rats and mice, and persistent hyaloid vessels are commonly noted during fundic examination. Other conditions reported in rats include glaucoma, cataracts, and coloboma.

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ADMINISTRATION OF DRUGS AND FORMULARY

Few drugs used in clinical practice are approved specifically in the US by the Food and Drug Administration for use in rabbits and rodents, a consideration that presents both legal and therapeutic complications (Tables 3.11 and 3.12). Apart from shortcomings resulting from interspecies extrapolations and limited clinical trials, several factors influence the pharmacologic effects of any given drug. Sex, strain or breed, age, diet, health status, time of day, breeding status, metabolic rate, presence of pathogenic organisms among intestinal flora, and nutritional level of the subjects, as well as composition of the bedding, experimental protocol, concomitant administration of other drugs, type of caging, and ambient temperature, all can affect a therapeutic outcome. In experimental studies, the use of antimicrobials and other drugs should be carefully evaluated to ensure that any potentially confounding effects of the drug will not interfere with the experiment and ultimately render the animal useless. In addition to these concerns, some drugs that are safe and efficacious in other animals are toxic in rabbits or rodents or will change an active, clinical infection to a chronic, subclinical, carrier state.

Antimicrobial therapy should include consideration of microbial sensitivity, cost of treatment, toxicity of the therapeutic agent to animals, toxicity of the antimicrobial to humans from ingestion of rabbit meat or handling the agent, public health significance of the pathogen involved, compatibility with other drugs or fluids, and the experimental protocol of the research study.

Fatal reactions to antimicrobial administration are a major concern in the therapy of rabbit, guinea pig, chinchilla, gerbil, and hamster diseases, particularly with oral beta lactam antimicrobials (penicillins and cephalosporins), some macrolides (erythromycin), and lincosamides (lincomycin and clindamycin). An alteration in normal enteric flora (dysbiosis) may occur, followed by clostridial or coliform proliferation, and subsequent release of toxins into the cecum. Deaths from enterotoxemia begin within 48 hours of initiating antimicrobial therapy and can continue for a week or more. The morphologic effect caused by oral doses of at least 10,000 U of penicillin G is a hemorrhagic typhlitis and colitis. Not all treated animals die after drug administration and omnivorous rodents such as rats and mice are resistant to these side effects. Some of these antimicrobial agents may still be administered by injection or for local treatment (packing in odontogenic abscesses). Many other antimicrobials have been associated with fatal enterotoxemias in rabbits and rodents, and even those considered safe can sometimes cause problems. Note that azithromycin, a macrolide antimicrobial, is generally considered safe to use in most species.

Aminoglycosides (streptomycin, dihydrostreptomycin, gentamicin, amikacin, neomycin, kanamycin, and tobramycin) can cause an ascending flaccid paralysis with respiratory arrest, coma, and death. The effects are due to neuromuscular blockade of skeletal muscle as aminoglycosides are thought to be calcium channel blockers. This reaction occurs most commonly when the drug is given at high doses, but anesthesia may be a predisposing factor. All members of the family are also potentially nephrotoxic and ototoxic. Gentamicin-induced retinal toxic effects may occur in rabbits after intravitreal injection of the drug. Streptomycin is frequently toxic in gerbils.

Although generally safe in rabbits and rodents, quinolone antibiotics (e.g., enrofloxacin, marbofloxacin) may cause arthropathies in young animals. Many bacteria infecting these species are highly sensitive to chloramphenicol. Chloramphenicol has rarely been associated with non-dose-dependent irreversible aplastic anemia in humans and appropriate directions for hand washing after handling must be given when this antibiotic is dispensed.

Often there is limited information available on species-specific pharmacokinetics of certain drugs for rabbits and rodents, and dosages must be extrapolated from those used for dogs and cats. Several approaches exist to adjust drug dosages from one species to another. Linear extrapolations based on body weight alone tend to result in overdosing of larger animals and underdosing of smaller ones. If this method is selected, drug doses should be extrapolated from those used for ferrets or cats.

Methods such as allometric (metabolic) scaling take basal metabolic rate and surface area into consideration and are rooted in the concept that smaller species tend to have higher metabolic rates and organ blood flow rates. Comparisons of allometric scaling among these species give scaling ratios of 2.8 for a mouse, 1.5 for a hamster, 1.3 for a rat, 1.2 for a guinea pig, and 1.0 for a rabbit. Drugs that are best estimated by allometric scaling include antimicrobials, compounds that are not highly protein bound, and compounds that rely largely on renal elimination rather than hepatic metabolism. This method does not take into account species- or strain-specific differences in specific hepatocellular metabolic pathways, which can't always be predicted based on animal size or rate of basal metabolism.

Another comparison for developing approximate drug dosages is surface area/body weight or surface area/body volume ratios, as these ratios tend to increase more gradually than changes in body weight alone. For example, surface-area-to-body-weight ratio comparisons are 5.7 for a mouse, 3.7 for a hamster, 2.5 for a rat, 1.7 for a guinea pig, and 1.0 for a rabbit. This calculation is particularly useful for estimating drug dosages for cancer chemotherapeutics.

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Table 3.11. Drug formulary for rabbits, guinea pigs, and chinchillas. (Caution: most uses and dosages are extralabel. Units are mg/kg unless otherwise specified.)

Drug	Rabbit	Guinea Pig	Chinchilla
Antimicrobials			
Amikacin	2–5 q8–12h SC,IM	2–5 q8–12h SC,IM	2–5 q8–12h SC,IM,IV
Ampicillin	Toxic	Toxic	Toxic
Azithromycin	15–30 q24h PO	15–30 q24h PO	15–30 q24h PO
Cefazolin	22 mg/kg IV intra-operatively		
Cephalexin	11–22 q8–12h PO,SC	50 q24h IM	
Chloramphenicol	30 q8–12h PO,SC,IM,IV	50 q12h PO,SC,IM	50 q12h PO,SC,IM
Chlortetracycline	50 q24h PO		50 q12h PO
Ciprofloxacin	5–20 q12h PO	7–20 q12h PO	5–15 q12h PO
Doxycycline	2.5 q12h PO	2.5 q12h PO	2.5 q12h PO
Enrofloxacin	5–10 q12h PO,SC,IM; 5 mg/kg IV intra-operatively.	5–10 q12h PO,SC,IM	10 q12h PO,SC,IM
Fluconazole	5 q24h PO		
Gentamycin	1.5–2.5 q8h SC,IM,IV	2–4 q8–12h SC,IM	2 q12h SC,IM,IV
Griseofulvin	25 q24h × 30–45 d PO	25–50 q12h × 14–60 d PO or 1.5% in DMSO for 5–7 d; topically	25 q24h × 30–60 d PO
Itraconazole	20–40 q24h PO	10–20 q24h PO	10–20 q24h PO
Lime sulfur dip	Dilute 1 : 40 with water, dip q7d for 4–6 wk	Dilute 1 : 40 with water, dip q7d for 4–6 wk	Dilute 1 : 40 with water, dip q7d for 4–6 wk
Marbofloxacin	2–5 q24h PO, IM, IV	2–5 q24h PO, IM, IV	2–5 q24h PO, IM, IV
Metronidazole	20 q12h PO, IV	20 q12h PO, IV	10–20 q12h PO, IV
Neomycin	30 q12h PO	12–16 q12h PO	15 q24h PO
Oxytetracycline	50 q12h PO		50 q12h PO
Penicillin G, benzathine	42,000–60,000 IU/kg q48h SC,IM	Toxic	Toxic
Penicillin G, procaine	42,000–60,000 IU/kg q24h SC,IM	Toxic	Toxic
Sulfadimethoxine	10–15 q12h × 10 d PO	10–15 q12h PO	25–50 q24h × 10–14 d PO
Sulfamethazine	1 mg/mL drinking water (dw)	1 mg/mL dw	1 mg/mL dw
Sulfaquinoxaline	1 mg/mL dw	1 mg/mL dw	
Terbinafine	10–30 mg/kg/day PO		
Tetracycline	50 q8–12 h PO or 250–1,000 mg/L dw	10–20 q8–12 h PO	0.3–2 mg/mL dw or 10–20 q8–12 h PO
Trimethoprim/sulfa	30 q12–24 h PO,SC,IM	15–30 q12h PO,SC	30 q12h PO,SC,IM
Tylosin	10 q12h PO,SC	10 q24h PO,SC; use with caution	10 q24h PO,SC
Vancomycin	50 q8h IV,IM		
Antiparasitic Agents			
Albendazole	7.5–20 × 3–14 d PO		25 q12h × 2 d PO
Amprolium (96% oral solution)	0.5 mL/500 mL dw × 10 d		
Amitraz		0.3% solution q7 d topically	
Carbaryl powder 5%	Twice weekly	Topically q7d × 3 wk	In dust q7d × 3 wk
Fenbendazole	10, repeat in 2 wk., prn PO, or 50 ppm in feed × 2–6 wk. 10–20 q24h for 28 days (*E. cuniculi*)	20 q24h × 5 d PO	20 q24h × 3–5 d PO

(*continued*)

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Table 3.11. ***(continued, Units are mg/kg unless otherwise specified)***

Drug	Rabbit	Guinea Pig	Chinchilla
Antiparasitic Agents (*continued*)			
Fipronil	Toxic	3 ml/kg	3 ml/kg
Imidacloprid	1 cat dose q30d, topical 0.1 ml/kg (advantage multi)	0.1 ml/kg (advantage multi)	0.1 ml/kg (advantage multi)
Ivermectin	0.4 q7–14d PO,SC	0.2–0.5 q7d × 3 wk PO,SC	0.2 q7d × 3 wk PO,SC
Lime sulfur	2–3% dip q7d × 4–6 wk	Dilute 1 : 40 in water, dip q7d × 6 wk	
Lufenuron	30 q30d PO		
Metronidazole	20 q12h PO	10–40 q24h PO	50–60 q12h × 5 d PO
Monensin	0.002–0.004% in feed		
Piperazine	200 mg/kg, repeat in 2–3 wk. or 2–5 mg/mL dw × 7 d	2–5 mg/mL dw for 7 d, off 7 d, repeat	100 q24h × 2 d PO
Praziquantel	5–10 repeat in 10 d PO,SC,IM	6–10 PO	5–10 repeat in 10 d PO,SC,IM
Pyrantel pamoate	5–10 repeat in 2–3 wk PO		
Pyrethrin shampoo or powder	Weekly × 4–6 wk	Weekly × 3 wk	Weekly × 3 wk
Selamectin	Dose revolution cat/kitten (20–30 mg/kg)	Dose revolution cat/kitten	Dose revolution cat/kitten
Sulfadimethoxine	50 once then 25 q24h × 10–20 d PO	25–50 q24h × 10 d PO	25–50 q24h × 10 d PO
Sulfamethazine	100 q24h PO, or 0.77 g/L dw or 0.5–1% in feed		
Sulfaquinoxaline	0.04–0.1% dw or 125–250 ppm in feed		
Thiabendazole	25–50 PO	100 q24h × 5 d PO	50–100 q24h × 5 d PO
Toltrazuril	10 mg/kg PO		
Miscellaneous			
Activated charcoal	1 g/kg	1 g/kg	1 g/kg
Cholestyramine	2 g/animal q24h PO		
Deslorelin acetate	4.7 mg SC implant	4.7 mg SC implant	4.7 mg SC implant
Dexamethasone	0.1–0.5 mg/kg, use caution	0.1–0.5 mg/kg	0.1–0.5 mg/kg
Dopamine	5–30 µg/kg/min (ineffective in rabbits)	5–15 µg/kg/min	5–15 µg/kg/min
Enalapril	0.1–0.5 q24h PO	0.1–0.5 q24h PO	0.1–0.5 q24h PO
Famotidine	0.5 q12h PO, SC, IV	0.5 q12h PO, SC, IV	0.5 q12h PO, SC, IV
Furosemide	1–5 q6-12h PO, SC, IV	1–5 q6-12h PO, SC, IV	1–5 q6-12h PO, SC, IV
Hydroxyzine	2 q12h PO	2 q12h PO	2 q12h PO
Levetiracetam	20 q8h PO	20 q8h PO	20 q8h PO
Lidocaine	50–100 µg/kg/min CRI (gastric stasis)	50–100 µg/kg/min CRI	50–100 µg/kg/min CRI
Meclizine	2–12 q24h PO		
Methimazole		0.5–2 q12–24 PO	
Metoclopramide	0.5–1 q6-12h PO	0.5–1 q6-12h PO	0.5–1 q6-12h PO
Norepinephrine	0.05–0.2 µg/kg/min	0.05–0.2 µg/kg/min	0.05–0.2 µg/kg/min
Ranitidine	2–5 q12h SC, IV		
Simethicone	1 ml/animal	0.5–1 ml/animal	0.5–1 ml/animal
Trimebutine	5–10 q12h	5–10 q12h	5–10 q12h

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Table 3.12. Drug formulary for hamsters, gerbils, mice, and rats. (Caution: most uses and dosages are extralabel. Units are mg/kg unless otherwise specified.)

Drug	Hamster	Gerbil	Rat	Mouse
Antimicrobials				
Amikacin	2–5 q8–12h SC	2–5 q8–12h SC	10 q12h SC	10 q8–12h SC
Ampicillin	Toxic	6–30 q8h PO	20–100 q12h PO,SC	20–100 q12h PO,SC or 500 mg/L dw
Amphotericin B	1 mg/animal q12h × 5 d/wk × 3 wk SC			
Cephalexin		25 q24h SC	15 q12h SC	60 q12h PO
Cephaloridine	10–25 q24h SC	30 q12h IM	10–25 q24h SC	10–25 q24h SC
Cephalosporin				30 q12h SC
Chloramphenicol	50–200 q8h PO, or 30–50 q12h SC	50–200 q8h PO, or 30–50 q12h SC	50–200 q8h PO, or 30–50 q12h SC	0.5 mg/mL dw or 50–200 q8h PO, or 30–50 q12h SC
Chlortetracycline	20 q12h PO,SC			25 q12h PO,SC
Ciprofloxacin	7–20 q12h PO	7–20 q12h PO	7–20 q12h PO	7–20 q12h PO
Doxycycline	2.5 q12h PO	2.5 q12h PO	5 q12h PO	2.5–5 q12h PO
Enrofloxacin	0.05–0.2 mg/mL dw × 14 d or 5–10 q12h PO SC	0.05–0.2 mg/mL dw × 14 d or 5–10 q12h PO SC	0.05–0.2 mg/mL dw × 14 d or 5–10 q12h PO SC	0.05–0.2 mg/mL dw × 14 d or 5–10 q12h PO SC
Erythromycin			20 q12h PO	20 q12h PO
Gentamicin	5 q24h SC	2–4 q8h SC	5–10 divided q8–12h	2–4 q8–12h SC
Griseofulvin	25–50 q12h × 14–60 d PO, or 1.5% in DMSO for 5–7 d; topically	25–50 q12h × 14–60 d PO, or 1.5% in DMSO for 5–7 d; topically	25–50 q12h × 14–60 d PO, or 1.5% in DMSO for 5–7 d; topically	25–50 q12h × 14–60 d PO, or 1.5% in DMSO for 5–7 d; topically
Ketoconazole	10–40 q24h × 14 d PO	10–40 q24h × 14 d PO	10–40 q24h × 14 d PO	10–40 q24h × 14 d PO
Metronidazole	7.5 mg/70–90 gm animal q8h	7.5 mg/70–90 gm animal q8h	10–40 q24h PO	2.5 mg/mL dw × 5 d or 20–60 q8–12h PO
Neomycin	0.5 mg/mL dw or 100 q24h PO	2.6 mg/mL dw or 100 q24h PO	2.6 mg/mL dw or 25 q12h PO	2.6 mg/mL dw
Oxytetracycline	0.25–1 mg/mL dw or 16 q24h SC	0.8 mg/mL dw or 10 q8h PO, or 20 q24h SC	0.4 mg/mL dw or 10–20 q8h PO	0.4 mg/mL dw or 10–20 q8h PO
Sulfadimethoxine	10–15 q12h PO	10–15 q12h PO	10–15 q12h PO	10–15 q12h PO
Sulfamerazine	1 mg/mL dw	0.8 mg/mL dw	1 mg/mL dw	1 mg/mL dw or 500 mg/L dw
Sulfamethazine	1 mg/mL dw	0.8 mg/mL dw	1 mg/mL dw	1 mg/mL dw
Tetracycline	0.4 mg/mL dw or 10–20 q8–12h PO	2–5 mg/mL dw or 10–20 q8–12h PO	2–5 mg/mL dw or 10–20 q8h PO	2–5 mg/mL dw or 10–20 q8h PO
Trimethoprim/sulfa	15–30 q12–24 h PO,SC	30 q12–24 h PO,SC	15–30 q12h PO,SC	30 q12h PO,SC
Tylosin	2–8 q12h SC,PO, or 0.5 mg/mL dw	0.5 mg/mL dw or 10 q24h PO,SC	0.5 mg/mL dw or 10 q24h PO,SC	0.5 mg/mL dw or 10 q24h PO,SC
Vancomycin	20 × 3+ mo PO			

(*continued*)

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Table 3.12. ***(continued, Units are mg/kg unless otherwise specified)***

Drug	Hamster	Gerbil	Rat	Mouse
Antiparastitic Agents				
Amitraz	1.4 mL/L water using cottonball application q14 d for 3–6 tx	1.4 mL/L water using cottonball application q14 d for 3–6 tx		
Carbamate(5%)	Twice weekly		Twice weekly	Twice weekly
Fenbendazole	20 q24h × 5 d PO	20 q24h × 5 d PO	20 q24h × 5 d PO, or 150 mg/kg feed for 7 d on, 7 d off for 3 tx	20 q24h × 5 d PO, or 150 mg/kg feed for 7 d on, 7 d off for 3 tx
Fipronil	7.5 q30–60 g topically		7.5 q30–60 g topically	7.5 q30–60 g topically
Ivermectin	0.2–0.4 q7–10 d × 3 tx PO,SC		0.2–0.4 q7–10d × 3 tx PO,SC	0.2–0.5 q7d × 3 wk. PO SC topically
Mebendazole			40 q7d × 21 d	40 q7d × 21 d
Metronidazole			10–40 mg/animal or 2.5 mg/mL dw × 5 d	30–40 q8–12h PO
Moxidectin				0.5 mg/kg of 0.5% pour-on applied to dorsum
Niclosamide		1 mg/10 gm PO		
Permethrin			0.25% dust in cage or cottonball soaked in 5% solution in cage for 4–5 wk	4 g of 0.25% dust once weekly in bedding for 4 wk
Piperazine citrate	2–5 mg/mL dw × 7 d, off 7 d, then repeat	2–5 mg/mL dw × 7 d, off 7 d, then repeat or 20–60 mg/100 gm PO	2–5 mg/mL dw × 7 d, off 7 d, then repeat	2–5 mg/mL dw × 7 d, off 7 d, then repeat
Pyrantel pamoate	50 PO	50 PO		
Praziquantel	6–10 PO	30 q14d × 3 tx PO	6–10 PO	6–10 PO, or 140 ppm in feed for 5 d
Pyrethrin powder	3×/wk × 3 wk	3×/wk × 3 wk	3×/wk × 3 wk	3×/wk × 3 wk
Thiabendazole	100–200 PO	100 q24h × 5d PO	100–200 PO	100–200 PO, or 0.3% in feed for 7–10 d, use repeated tx

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ANESTHESIA

This section describes anesthetics commonly available in veterinary clinics or research animal facilities. Anesthetics used frequently outside the US but not yet licensed for use in the country (e.g., Hypnorm—fentanyl plus fluanisone) are noted briefly. Refinement of anesthetic techniques in laboratory animal practice has resulted in a plethora of commercially available species- and size-specific anesthetic equipment for rabbits and rodents, including induction chambers, face masks, platforms to facilitate endotracheal intubation, nonrebreathing anesthetic circuits, downdraft tables, rodent ventilators, heating mats, pulse oximeters, and other small mammal monitoring equipment.

Many factors affect the response of rabbits and rodents to anesthetics. Such factors include sex, age, species, strain, weight, percent body fat, health and nutritional status, ingesta content, time of day, genetic background, type of bedding, environmental temperature during recovery, cardiovascular and respiratory system effects, and respiratory and metabolic rates. The large, ingesta-filled ceca of rabbits and guinea pigs may result in overdosing due to an overestimation of the true body weight. For nocturnal species, drug-induced sleeping times will be longer in the afternoon, when hepatic metabolic activity is at low ebb.

Cedar and pine bedding emit volatile oils, such as pinenes that, over time, activate hepatic cytochrome P450 metabolizing enzymes. This may lead to increased rates of metabolism for drugs that are transformed by these systems, such as various anesthetics and analgesics, and as a result, reduced efficacy and sleeping times when these agents are given to animals housed on these beddings. Kiln drying of softwood shavings at high temperatures may eliminate many of these volatile oils.

Most anesthetics cause a dose-dependent depression of physiologic homeostasis, including cardiovascular, respiratory, and thermoregulatory systems. The physiologic changes can vary considerably with different anesthetics. Interpretation and appropriate response to the various parameters measured requires experience and training with the anesthetic regimen and the species being anesthetized. The level of sensibility, analgesia, and functioning of the cardiovascular (including fluid balance), respiratory, and thermoregulatory systems are used to assess the adequacy of the anesthetic regimen.

Loss of sensibility occurs at a light plane of anesthesia and is sufficient for purposes of restraint or minor noninvasive procedures. Sensibility is lost before loss of pain perception occurs, and at a light anesthetic plane, can be regained by painful stimuli.

Lack of response to painful stimuli occurs at a surgical stage of anesthesia. Prior to surgery, adequate pain management should be ascertained by the presence or absence of various reflexes (described below). Individual animal responses vary widely, and a single reflex response may not be adequate for assessing the surgical plane of anesthesia or the level of analgesia.

Preoperative Procedures

Animals in poor clinical condition require stabilization prior to anesthesia and surgery. Obesity and old age, which are common conditions in companion animals, will increase anesthetic risk. Candidates for anesthesia and surgical procedures should, if possible, be free from respiratory disease. Withholding food for long periods from rabbits and rodents is not necessary as they are unable to vomit, although they can passively regurgitate if their stomach is full and they are placed on their back. In larger species, such as chinchillas, guinea pigs, and rabbits, food may be withheld for 4–6 hours to reduce the volume of the gastrointestinal tract and clear the mouth. Food should not be withheld from small rodents for more than 2–3 hours because of the possibility of hypoglycemia and dehydration, as these species typically will not drink if they do not eat. Potable water should always be available to small mammal patients up to the time of anesthetic induction. Preoperative administration of warm, subcutaneous fluids,

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such as lactated Ringer's solution, at 10 mL/kg may be beneficial in debilitated small rodents.

Premedication with analgesics and/or sedatives may facilitate and potentiate induction. Placement of intravenous catheters and clipping of surgical areas can often be performed during this time, which will decrease overall anesthetic time and allow the use of intravenous injections for anesthetic induction. Typical protocols that have proven to be very safe in rabbits and rodents include midazolam-opioid-(ketamine) combinations (see below for dosages). Acepromazine is fairly safe even in debilitated animals and can be used intramuscularly or subcutaneously at doses of 1–2 mg/kg in rabbits and 0.5–1 mg/kg in rats, mice, hamsters, chinchillas, and guinea pigs. Acepromazine should be avoided in gerbils, many of which suffer from hereditary epilepsy, as it reduces the seizure threshold. Hypnorm (fentanyl/fluanisone), if available, at 0.1 mL/kg for rabbits, 0.08 mL/kg for rats, and 0.2 mL/kg for guinea pigs given IM 15 to 20 minutes prior to induction may help prevent breath holding during gas anesthesia. It is quite irritating and larger doses should be divided into two or more sites to prevent post-injection lameness. Hypnorm can be reversed with butorphanol at 0.2 mg/kg or buprenorphine at 0.05 mg/kg IV or IM.

In some cases, such as when bradycardia has been diagnosed, administration of glycopyrrolate or atropine sulfate administered subcutaneously 30 minutes before anesthesia may be indicated. Glycopyrrolate does not cross the blood–brain barrier and is more effective blocking drug-induced bradycardia in rabbits and rodents, compared with atropine. Some rabbits and rodents produce plasma atropine esterase, which hydrolyzes and inactivates atropine. Glycopyrrolate may be preferred for this reason, but if atropine is to be used, the dose may need to be increased or administered at more frequent intervals to achieve the desired effect. The level of atropine esterase activity further depends on season of year and the sex, strain, age, and weight of rabbit or rodent.

Anesthetic Administration

Because many small mammal companions have subclinical respiratory disease that results in hypoventilation and mild respiratory compromise, preoxygenation with 100% O_2 for 3–5 minutes prior to anesthetic induction may be useful to minimize hypoxemia associated with anesthetic-induced apnea. Preoxygenation may also help to reduce breath-holding and subsequent apnea often seen in rabbits induced with gas anesthetics, such as isoflurane.

Mask induction with either isoflurane or sevoflurane is commonly performed in rabbits and larger rodents. The animal should be restrained gently but firmly during induction and induced as quickly as possible. Use of a towel wrap facilitates restraint in rabbits (see Figure 2.11). In rabbits and guinea pigs in particular, sudden death has been reported during gas anesthesia induction when animals are highly excited or are permitted to struggle. It is hypothesized that sudden catecholamine release from the adrenal glands during excitement and struggling may lead to coronary vessel constriction, acute cardiac ischemia, and sudden death. During mask induction, the entire head of the rabbit or rodent can be placed within an appropriately sized cone mask and the inhalant turned to maximum (5% for isoflurane). Rabbits and some rodents typically go through different stages during mask induction: an initial quiet phase, an excitation phase, a breath-holding phase, and a maintenance phase. Reducing the vaporizer setting before rabbits are fully anesthetized may lengthen breath-holding and induction periods, so should be avoided. Switching to a smaller mask over the nose once the excitation phase is over will optimize inhalant gas delivery and limit CO_2 rebreathing, as will intubation or use of a laryngeal mask airway (LMA) (described below). The minimum alveolar concentration (MAC) required for rabbits is higher than most other mammals (around 2–2.2% for isoflurane and 3.7% for sevoflurane), whereas rodents have a similar MAC for both agents. As the excitation phase is strong in rabbits, chamber induction is not recommended to avoid animal injury.

Induction of inhalant anesthesia in small rodents is facilitated by use of an induction chamber, with an appropriate scavenging system to minimize exposure of personnel to waste gases (Figure 3.31). The induction chamber should be as small as possible to adequately accommodate the animal with minimal dead space. Several commercially available chambers are available, or clear plastic containers with lids and rubber gasket seals may be modified for this purpose. Small rodents also may be induced by using a large face mask to completely cover their body, mimicking an induction chamber.

Once induced, the animal is quickly removed from the chamber, and either intubated or placed on a face mask and attached to a nonrebreathing anesthetic circuit for maintenance (Figure 3.32). In all cases, a downdraft table or other appropriate scavenging system should be used to protect personnel from inhaling waste gases while ensuring that animals continue to breath the anesthetic vapor in the carrier gas.

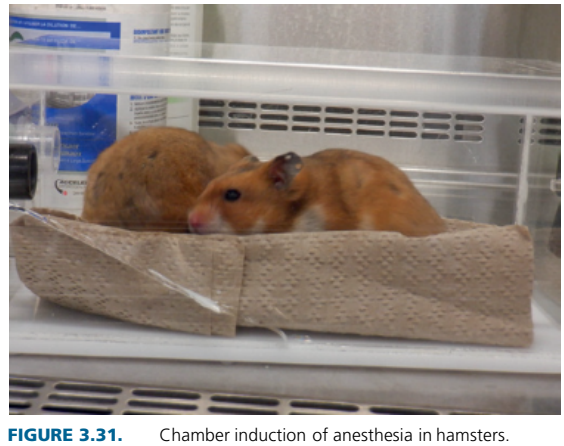


FIGURE 3.31. Chamber induction of anesthesia in hamsters.

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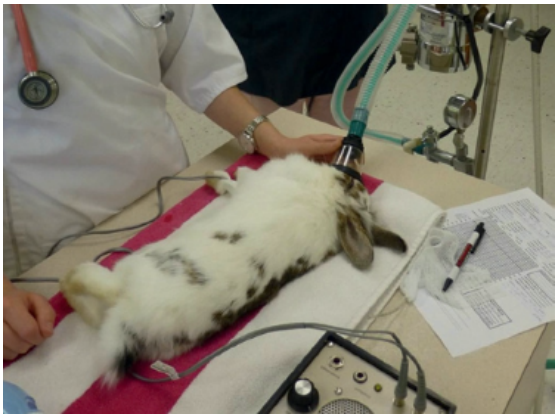


FIGURE 3.32. Monitoring of anesthesia maintenance in a rabbit following induction. Courtesy of Calgary Avian & Exotic Pet Clinic.

For animals with an intravenous catheter in place (typically companion rabbits and some guinea pigs and chinchillas), intravenous induction is preferred as it is smoother, the breath-holding phase is limited, and intubation is more quickly achieved. Propofol and alfaxalone are frequently used and dosages in rabbits are much larger than for other companion mammals. These drugs must be given slowly to limit apnea, and oxygen must be concurrently administered. Propofol or alfaxalone are usually given at a dose of 8–15 and 5–10 mg/kg, respectively. Ketamine and midazolam induction is another option at a dose of 5/0.5–1 mg/kg, IM, respectively, after premedication with the same drugs (2–3/1–2 mg/kg, IM, respectively). Dosages are summarized in Table 3.13.

Other injectable anesthetics may be given under the skin folds on the back of the neck (SC), deeply into the hindlimb or epaxial muscles (IM), or into the peritoneal cavity (IP). Intramuscular (IM) injections should be avoided in small rodents because of the potential for pain upon injection, subsequent sloughing of skin and muscle due to drug-induced necrosis, and the possibility of self-mutilation when acidic or irritating agents are injected. Intraperitoneal (IP) injections are given by sharp puncture at a 60° angle with an appropriate-sized needle in the lower right abdominal quadrant while firmly restraining the animal in a head-down position (Figure 3.33).

Ketamine is preferably given SC or IP to small rodents because of muscle irritation upon intramuscular injection. Aspirating the syringe before injection will help to ensure that the anesthetic is administered into the peritoneal cavity and not into organs or blood vessels. Because of their large cecum, it has been estimated that 20% of IP injections in guinea pigs inadvertently penetrate abdominal organs. Prolonged induction and recovery times may be indicative of injection of the anesthetic into a visceral organ. The subcutaneous route is more accurate than IP administration and can be used as an alternative in most cases. Dosages and body weights should be determined accurately to avoid fatalities in these small mammal species.

Because of the large eye size, rodent and rabbit palpebrae may not close completely during anesthesia. Sterile, nonmedicated ophthalmic drops or ointment should be used on all patients to minimize corneal drying (Figure 3.34). Temporary tarsorrhaphy using micropore tape is recommended in rabbits for long procedures. Patients should be positioned carefully to avoid direct contact of the cornea with the heating pad or blanket (Figure 3.35). Oxygen should be given by face mask during injectable anesthesia to counteract drug-induced hypoxemia and possible corneal injury.

Endotracheal Intubation

Rabbits and rodents rarely regurgitate and can be anesthetized without endotracheal intubation for a multitude of surgical procedures such as basic dentistry, lumpectomies, and routine spay and neuter procedures. However, intubation is recommended in rabbits for longer anesthesia and all abdominal surgeries. As rodents are significantly harder to intubate, they may be kept on a mask if intubation attempts are unsuccessful. In addition, for surgical procedures involving thoracotomies, those disrupting respiratory neuromuscular signaling, head surgeries, or when required for research purposes, endotracheal intubation may be advisable. Animals should be induced and intubated after cough and swallowing reflexes are abolished. For rabbits, propofol administered via an IV catheter at a dose of 8–15 mg/kg by slow bolus, then topped up with additional propofol to effect, may assist with initial induction and relaxation in preparation for intubation. Relaxation of the jaw musculature signifies that the animal is anesthetized sufficiently to begin intubation. The mouths of rabbits and rodents do not open widely, and the larynx is difficult to see. Topical anesthetic (e.g., lidocaine) should not be sprayed into the oral cavity of small rodents because of the danger of asphyxiation, irritation, and toxicity; however, it can be applied sparingly with a cotton swab to the soft palate and pharynx. Topical anesthesia to prevent laryngospasm in rabbits should be used cautiously before intubation because the anesthetic suppresses the convenient forward motion of the glottis during swallowing.

Intubation is not easy to accomplish in any of these species, especially in rodents. Care must be taken to obtain customized equipment and to practice and master the technique to avoid traumatizing the sensitive oral and respiratory structures. The large fleshy tongue of these species, large teeth, deep, narrow oral cavity, and small mouth complicate the process. The palatal ostium in the guinea pig and chinchilla further obscures the epiglottis. For rabbits, commercially available 2.0–3.5 uncuffed endotracheal tubes cut to a suitable length to minimize dead space can be used for most adult animals. Animals should be lightly anesthetized in sternal recumbency with hyperextension of the neck before attempting the procedure. There are many different intubation techniques described, which may involve either a blind

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Table 3.13. Suggested drugs and dosages for rabbit preanesthetic medication and induction. (Caution: most uses and dosages are extralabel.)

Drug(s)	Dosage	Route	Comments
Acepromazine Combinations			
Acepromazine	1–5 mg/kg	IM	Mild-to-moderate sedation
Acepromazine	0.1 mg/kg	IM	Premedication; acepromazine may prolong recovery
+butorphanol	+0.4 mg/kg	IM	
Acepromazine	0.1 mg/kg	IM	Premedication; acepromazine may prolong recovery
+hydromorphone	+0.2 mg/kg	IM	
Alfaxalone Combinations			
Alfaxalone	5–10 mg/kg	IV	Induction; administer via IV cannula slowly over 60 seconds; support with oxygen
Alfaxalone	2.5–6 mg/kg	IM	Mild sedation for ~½–1 h, depending on dose; short excitement period after injection; ataxia and nystagmus during recovery; respiratory depression and hypoxemia; support with oxygen
Alfaxalone	2–3 mg/kg	IV	Premedication with buprenorphine IM prior to IV
+buprenorphine	0.03 mg/kg	IM	alfaxalone for induction; support with oxygen.
Alfaxalone	4 mg/kg	IM	Moderate sedation for ~40 min; support with oxygen
+buprenorphine	0.03 mg/kg	IM	
Alfaxalone	6 mg/kg	IM	Moderate sedation for ~¾ h; support with oxygen
+butorphanol	0.3 mg/kg	IM	
Alfaxalone	6 mg/kg	IM	Deep sedation for ~2½ h with anesthesia for ~1 h;
+butorphanol	0.3 mg/kg	IM	support with oxygen
+dexmedetomidine	0.2 mg/kg	IM	
Alfaxalone	2 mg/kg	IM	Sedation; butorphanol and midazolam given in same
+butorphanol	1 mg/kg	IM	syringe, alfaxalone given in a separate syringe
+midazolam	1 mg/kg	IM	
Alfaxalone	6 mg/kg		Deep sedation; provides ~2½ h of sedation
+dexmedetomidine	0.2 mg/kg		
Alfaxalone	3 mg/kg	IV	Premedication with droperidol and fentanyl 15 min
+droperidol	0.625 mg/kg	IM	before IV induction with alfaxalone; alfaxalone given
+fentanyl	0.0125 mg/kg	IM	over 60 s. Respiratory depression and hypoxemia occur without oxygen supplementation.
Alfaxalone	4 mg/kg	IM	Mild sedation for painful procedures
+hydromorphone	0.1 mg/kg	IM	
Alfaxalone	6 mg/kg		Moderate sedation; provides ~1 h of sedation
+midazolam	1 mg/kg		
Buprenorphine	0.05 mg/kg	IV	Do not use with fentanyl constant rate infusion
Butorphanol	0.5–1 mg/kg	IV	Do not use with fentanyl constant rate infusion
Dexmedetomidine	0.2 mg/kg	IM	Moderate sedation for ~1½ h, bradycardia; recovery may be rough; can reverse with atipamezole
Diazepam	5–10 mg/kg	IM	Mild-to-moderate sedation
Fentanyl	2–5 ug/kg	IV	
Hypnorm Combinations			
Hypnorm (fentanyl/ fluanisone)	0.2–0.5 mL/kg	IM	Mild-to-heavy sedation for 30 to 60 min. May produce respiratory depression and hypoxia. Good analgesia from fentanyl. Can reverse fentanyl with 0.5 mg/kg butorphanol or 0.05 mg/kg buprenorphine IV, or in emergencies, naloxone at 0.1 mg/kg IM or IV.

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Table 3.13. ***(continued)***

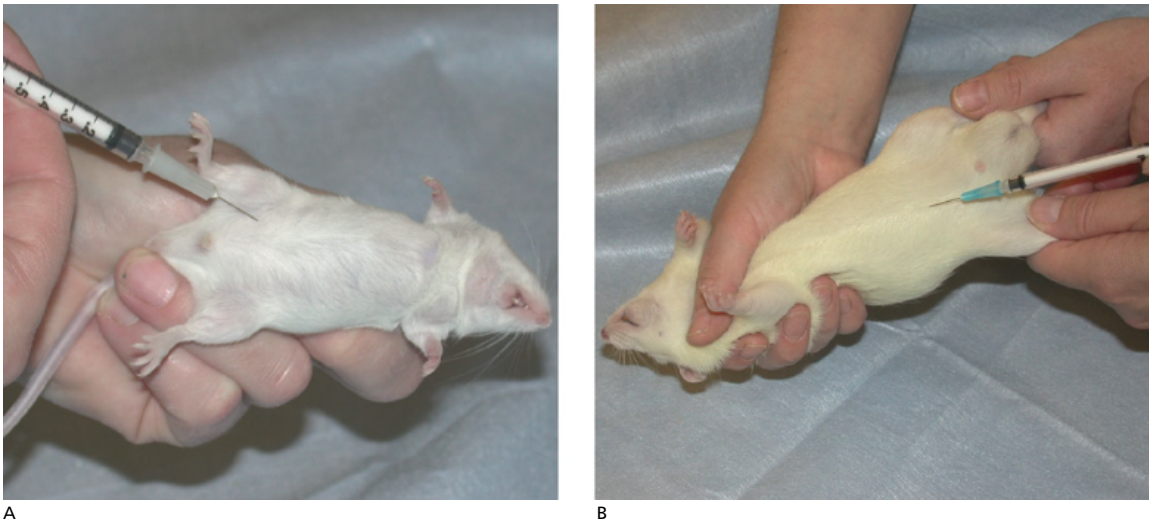
Drug(s)	Dosage	Route	Comments
Hypnorm (fentanyl/ fluanisone)	0.3 mL/kg	IP or IV	Provides anesthetic depth, good muscle relaxation and analgesia for 20 to 40 min. Do not mix drugs in same syringe. May produce respiratory depression and hypoxia. Can reverse fentanyl with 0.5 mg/kg butorphanol or 0.05 mg/kg buprenorphine IV, or in emergencies, naloxone at 0.1 mg/kg IM or IV.
+diazepam	2 mg/kg	IP or IV	
Hypnorm (fentanyl/ fluanisone)	0.3 mL/kg	IP or IV	Provides anesthetic depth good muscle relaxation and analgesia for 20–40 min. Drugs can be mixed in same syringe and given IM or IP, or give Hypnorm IM then midazolam given intravenously into the lateral ear vein 15 min later. May produce respiratory depression and hypoxia. Can reverse fentanyl with 0.5 mg/kg butorphanol or 0.05 mg/kg buprenorphine IV, or in emergencies, naloxone at 0.1 mg/kg IM or IV.
+midazolam	2 mg/kg	IP or IV	
Ketamine Combinations			
Ketamine	30 mg/kg	IM	Sedation
+acepromazine	1–2 mg/kg	IM	
Ketamine	5 mg/kg	IM	Sedation; butorphanol and midazolam given in same syringe, ketamine given in a separate syringe
+butorphanol	1 mg/kg	IM	
+midazolam	1 mg/kg	IM	
Ketamine	30 mg/kg	IM	Sedation; alpha 2 agonists can cause hypoxemia
+dexmedetomidine	0.025 mg/kg		
Ketamine	30 mg/kg	IM	Sedation
+diazepam	1 mg/kg	IM	
Ketamine	15–30 mg/kg	IM	Sedation
+midazolam	+1–3 mg/kg	IM	
Ketamine	0.5–2.5 mg/ kg	IV	Induction after IM premedication; maintain on iso
+midazolam	+0.13–5 mg/ kg	IV	
Ketamine	5–15 mg/kg	IM	Produces premedication to light anesthesia, use in fractious rabbits
+midazolam	+0.5–2 mg/kg	IM	
+hydromorphone	0.1–0.2 mg/ kg	IM	May use fentanyl instead
Ketamine	20 mg/kg	IM	Provides ~75 min of anesthesia with good analgesia
+midazolam	2 mg/kg	IM	
+xylazine	2 mg/kg	IM	
Ketamine	20–50 mg/kg	IM	Provides ~30 min of surgical anesthesia. Alpha 2 agonists can cause hypoxemia. Can reverse xylazine with 0.2 mg/kg yohimbine IV or 0.001 mg/kg atipamezole, SC, IV, or IP.
+xylazine	2 mg/kg	IM	
Ketamine	35 mg/kg		Provides up to 100 min of anesthesia. May cause depressed respiratory rate, heart rate, and especially blood pressure (may be critical in a hypovolemic patient).
+xylazine	3 mg/kg		
+ acepromazine	0.75 mg/kg		
Medetomidine Combinations			
Medetomidine	0.1–0.5 mg/ kg	IM; SC	Mild-to-deep sedation higher risks in debilitated patients; bradycardia
Medetomidine	0.15 mg/kg	IM	Provides ~25 min surgical anesthesia. Reverse medetomidine with 0.75 mg/kg atipamezole IM or IV.
+midazolam	1.0 mg/kg	IM	
+butorphanol	1.5 mg/kg	IM	

(*continued*)

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Table 3.13. ***(continued)***

Drug(s)	Dosage	Route	Comments
Midazolam Combinations			
Midazolam	0.5–2 mg/kg	IM, IV	Mild-to-deep sedation
Midazolam +hydromorphone	0.5–2 mg/kg +0.2 mg/kg	IM IM	Premedication
Midazolam +butorphanol	0.5–2 mg/kg +0.5–1 mg/kg	IM IM	Premedication
Midazolam +hydromorphone	0.5–2 mg/kg +0.1–0.2 mg/kg	IM IM	Premedication
Midazolam +fentanyl	0.5–2 mg/kg +5 µg/kg	IM IM	Premedication
Propofol	8–15 mg/kg	IV	Induction
Propofol	12.5 mg/kg	IV/IO	Induction; slowly over 10 s; provides ~4 minutes of anesthesia
Xylazine	2–5 mg/kg	IM	Mild-to-moderate sedation, some analgesia, higher risks in debilitated patients



A B

FIGURE 3.33. Technique for intraperitoneal injection into a mouse (A) and rat (B).

procedure that relies on the sound of airflow as the tube is passed into the trachea or direct observation of the larynx with a specialized laryngoscope, rigid endoscope, or otoscopic cone with a side opening.

The anatomy and technique can be reviewed and practiced on inanimate animal models or cadavers. Care should be taken not to bend the head too far dorsally because cervical vertebral fracture may occur. Endotracheal tubes for rodents may be custom-made from appropriately sized and modified IV catheters.

More than two to three attempts at intubation may result in epiglottal hemorrhage and trauma. Respiratory secretions accumulating during anesthesia may be removed by suction or cotton swabs. Rabbits have a highly vascularized submucosal plexus within the trachea. Movement of the head with the endotracheal tube in place or prolonged surgeries in intubated animals may result in postprocedural tracheal edema, fibrosis, and stenosis in rabbits. This is manifested clinically within 2–10 days following the procedure by tachypnea, inactivity, reduced food consumption, respiratory stridor, and cyanosis. Severely affected animals may die.

Laryngeal masks can also be used safely in rabbits (V-gel®) and may be developed for larger rodents in the future. They are reasonable alternatives to endotracheal intubation.

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FIGURE 3.34. Sterile ophthalmic lubricant being placed in the eye of an anesthetized guinea pig.

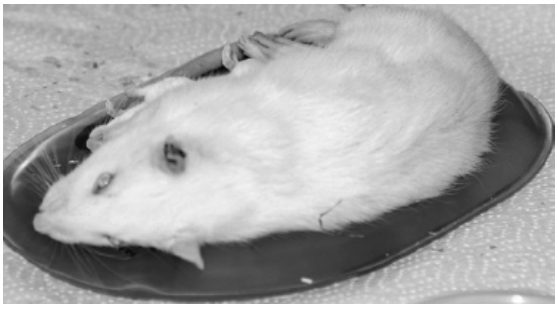


FIGURE 3.35. Microwavable gel pack for maintaining rodent body heat during anesthesia.

Anesthetic Overdose

Anesthetic overdose is indicated by diaphragmatic breathing, gasping, loss of various reflexes, and cyanosis. Severe cases may result in death. If the respiratory rate can be determined, a decrease to less than 40% of the normal rate indicates impending respiratory failure. Assuming a patent airway is present, artificial respiration, respiratory stimulants, or anesthetic antagonists can be used. Such drugs include doxapram (2–10 mg/kg IM or IV every 15–20 minute), naloxone (0.01–0.1 mg/kg IP, IM, or IV), nalorphine (1–5 mg/kg IV), levallorphan (0.45 mg/kg IV), flumazenil (0.05–0.2 mg/kg), yohimbine to reverse xylazine (0.2–1 mg/kg IM or IV), or atipamezole to reverse medetomidine (SC or IV administered at the same volume as medetomidine). Warmed, 37 °C (98.6 °F) isotonic saline can be given by IV or IP routes.

Gentle manual cardiopulmonary resuscitation via compression of the sternum 50–100 times/min or blowing with a Pasteur pipette bulb or tightly fitting face mask into the animal's nose may stimulate respiration, as may gently swinging the animal repeatedly or tipping the animal from horizontal to head down. Pressing the end of the nose between the nostrils with a blunt probe or the edge of a fingernail may stimulate the animal to take a breath. Oxygen should be supplied, if it is not already being given. Patients must be intubated or a laryngeal mask may be placed to secure airway in case of respiratory arrest. Emergency drugs and fluid resuscitation therapy must also be implemented. It is helpful to have drug dosages for individual patients precalculated and an emergency drug kit ready to save time during emergencies.

Supportive Care and Anesthetic Monitoring

It is critical that anesthetized rabbits and rodents be kept warm, well hydrated, and well oxygenated from induction through to recovery. Hypothermia decreases drug metabolism and elimination and may prolong anesthesia, sedation, and recovery, and promote hypotension. Because body heat loss and metabolic rate are related to the surface area to body weight ratio, loss of heat or decreased rate of metabolism of a drug is more rapid in mice than rabbits. Commercially available circulating warm water blankets, warm air blankets (such as the Bair Hugger®), and thermal pads designed with rectal temperature probes for feedback are available for small animals. Electrical heating pads, microwavable heat pads, water bags or bottles, and lamps should be used with extreme caution to prevent overheating, dehydration, or thermal burns. Animals should be insulated from stainless steel surfaces and covered with a light-weight drape, stockinette, or bubble-wrap whenever possible, taking care not to impede respiration. During recovery, oxygen-supplying incubators are helpful, and research animals of the same sex and species can be grouped together for additional warmth, when possible. Environmental temperatures of 30–35 °C (86–95 °F) for rodents and 25 °C (77 °F) for rabbits are appropriate. Patients should be monitored closely for overheating during recovery and should have the option of moving to a cooler area of the enclosure as they awaken.

Intraoperative monitoring of anesthetized animals may be accomplished using measures of arterial blood oxygen saturation (pulse oximetry) (Figure 3.36), body temperature, capnometry (for intubated animals), indirect or direct blood pressure (Figure 3.37), and electrocardiography. Respiratory alert monitors designed for larger small animal species may not detect the small volume of gas emitted during respiratory excursions of rabbits and rodents. Indirect blood pressure monitoring may not be reliable in these patients, so trends should be used instead of absolute values. In rabbits, arterial catheters in the central ear vein may be placed for direct arterial blood pressure monitoring. Oscillometric blood pressure measurements tend to be less reliable than Doppler-derived blood pressure in small patients.

Intraoperative fluids, preferably warmed to body temperature, such as Plasmalyte-A®, lactated Ringer's solution, or 0.9% saline (if metabolic alkalosis) can be given IV, SC, IP, or intraosseously (IO) at a rate of 5–10 mL/kg/hr (Figure 3.38). Commercially available fluid warmers can be used with IV extension sets, or tubing can be passed through a container of

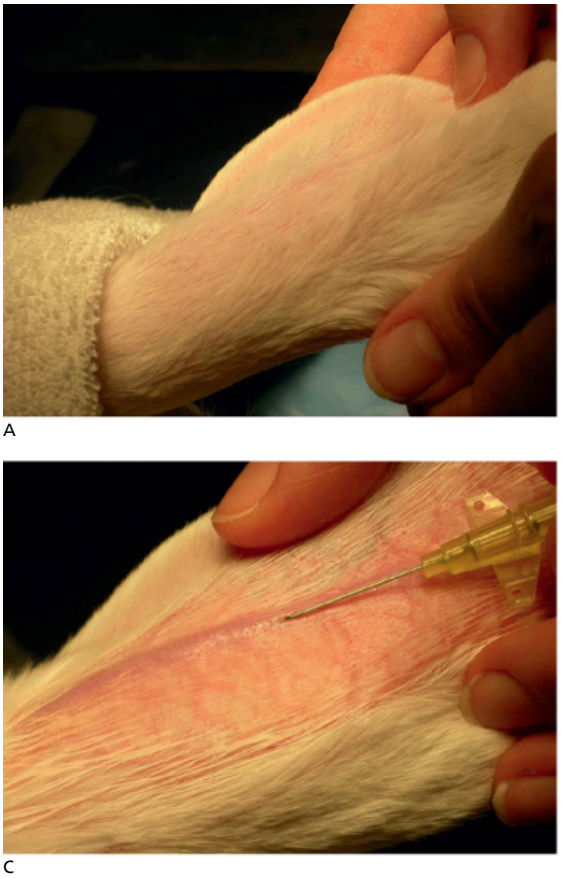
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FIGURE 3.36. Chinchilla anesthetized by isoflurane in oxygen, delivered by facemask. A pulse oximeter clamp is placed on the forelimb to monitor arterial blood oxygen saturation and a Doppler flow probe is taped over the jugular vein, giving an audible heart rate.

warm water. Intravenous catheters can easily be placed in rabbits (marginal ear, cephalic, or lateral saphenous veins) (Figures 3.39 and 3.40) and rats (saphenous and tail vein) and can often be placed in the cephalic or lateral saphenous vein of other rodents. Electronic or spring-driven syringe infusion pumps (e.g., Springfusor®) are useful for administering fluids to very small patients (Figure 3.41). Postoperative maintenance fluids are given at 40–80 mL/kg/d until it is certain that the animal is eating and drinking sufficiently. Rabbits are particularly susceptible to the hypotensive effects of isoflurane, especially when artificially ventilated. Therefore, the use of a balanced anesthesia protocol as well as vasopressors is important.

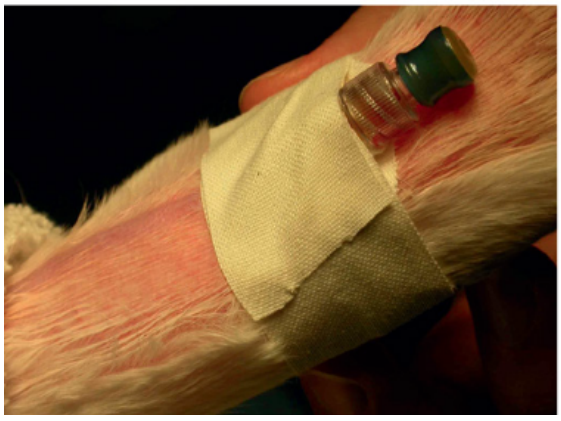
Breathing may be compromised in chinchillas, guinea pigs, and rabbits placed in dorsal recumbency, because of the weight of the large abdominal contents pressing on the relatively small thorax, especially in obese animals. Elevating the head and thorax will help prevent respiratory compromise. Administration of oxygen during anesthesia with injectable agents, especially ketamine and xylazine, is critical to avoid



A B C D

FIGURE 3.37. Sequence of events to catheterize the central auricular artery of the rabbit for direct blood pressure monitoring. Prior to plucking, the ear artery is not visible (A). After plucking the hair, the artery is readily seen (B). Following surgical preparation of the catheter site, a 25 g IV catheter may be introduced into the vessel and the stylet removed (C, D).

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E



F

FIGURE 3.37. *(continued)* The catheter is capped and flushed (E). To secure, the catheter is taped into place and a roll of cotton gauze is taped to the inside of the ear for stabilization of the catheter (F).



FIGURE 3.38. Lateral radiograph of a chinchilla with intraosseous catheter inserted into tibia.



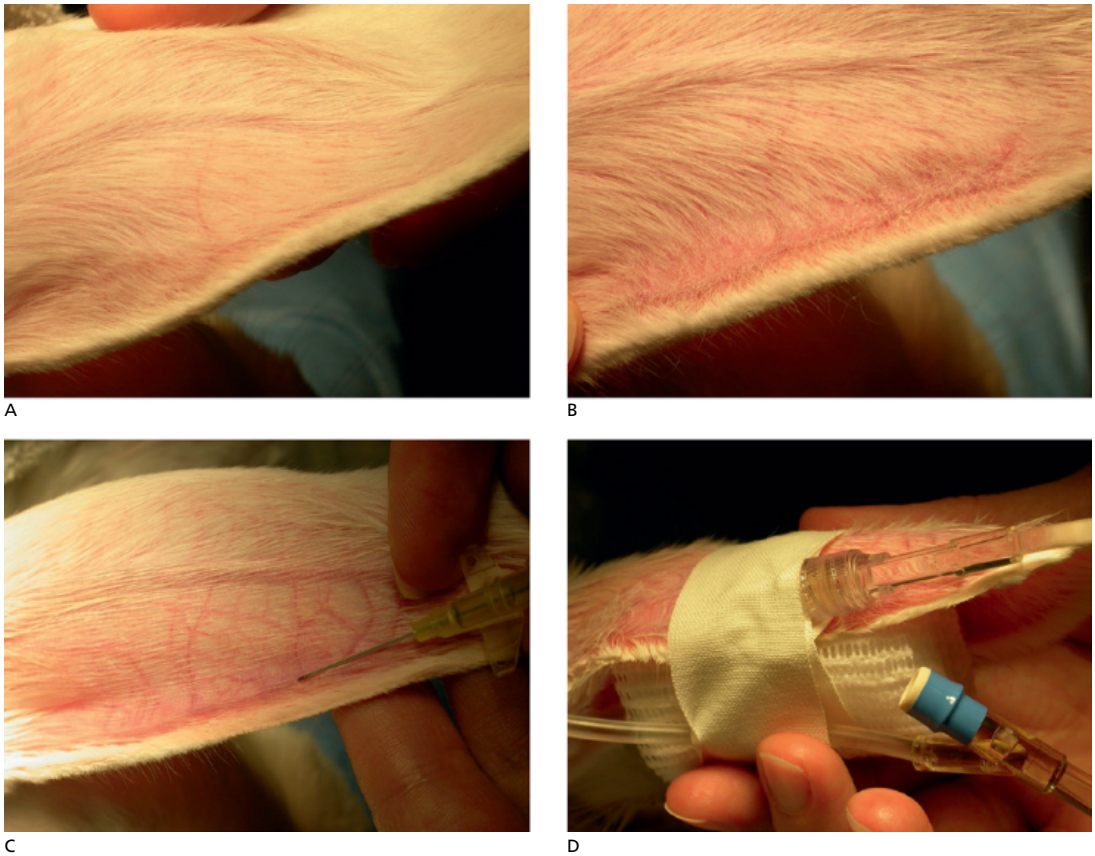
FIGURE 3.39. A cephalic catheter may be placed in the rabbit for fluid administration.

hypoxemia, which may predispose animals to corneal lesions and other problems. Cyanosis and pulse oximeter SpO_2 readings of <65% are often observed in spontaneously breathing rats anesthetized with injectable agents (Figure 3.42). The use of a ventilator is recommended in intubated patients with decreased ventilation or apnea under anesthesia.

Respiratory stimulants (e.g., doxapram) may be indicated in some circumstances, and appropriate analgesia must always be provided. Antimicrobials may be given to rats and mice when asepsis is not possible or is compromised. Antimicrobials should be used cautiously in species susceptible to dysbiosis and enterotoxemia. Prophylactic antimicrobials may be given depending on the surgery. Enrofloxacin 5 mg/kg IV or cefazolin 22 mg/kg IV are typically used in rabbits. Wounds should be attended to regularly and bedding changed as needed to keep the surgical site clean.

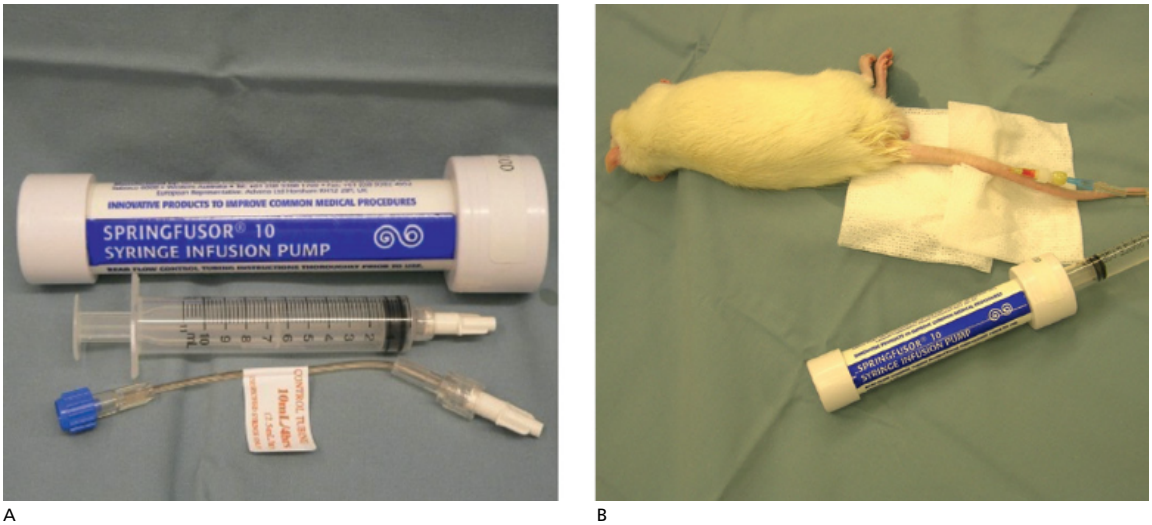
Postsurgical feeding and hydration are critically important. Subcutaneous or intravenous maintenance fluid

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A B C D

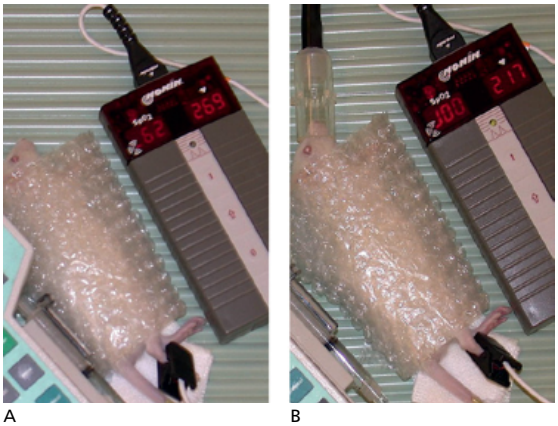
FIGURE 3.40. The marginal ear vein is a convenient site to catheterize for fluid delivery in rabbits. The vein is barely visible prior to plucking (A). Catheter placement and support is similar to that described for the auricular artery (B, C, and D).



A B

FIGURE 3.41. Fluids may be administered intravenously to rats using the lateral tail vein. A tourniquet applied to the base of the tail facilitates identification of the vessel. A Springfusor syringe infusion pump is a convenient means of providing ongoing IV fluids to small patients (A and B, see text).

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A B

FIGURE 3.42. When possible, oxygen supplementation should be provided to small rodents anesthetized with injectable agents to prevent hypoxemia. The rat depicted in this image has been anesthetized with a ketamine/xylazine combination. Pulse oximeter values are shown before (A) and after (B) oxygen supplementation by facemask. Arterial oxygen saturation levels less than 90% are considered to reflect hypoxia in an anesthetized patient.



FIGURE 3.43. Rat licking Ensure® from a syringe.

therapy is recommended in the post-operative period as well as assisted feeding in case of anorexia (with products such as Oxbow critical care herbivores®) (Figure 3.43). When possible, it is helpful to introduce the patient to the supplement prior to the procedure, so it is not entirely novel during the postoperative period. Provision of food and water on the cage floor, rather than in overhead containers, will facilitate access. Postsurgical deaths frequently result from anesthetic overdose, hypothermia, hypoxemia, fluid loss, gastrointestinal stasis, or acidosis. In animals susceptible to gastric stasis, a lidocaine constant rate infusion at 75–100 µg/kg/min, and further analgesics may be given during the recovery period.

Topical and Local Anesthesia

Lidocaine, bupivacaine, and other topical anesthetics may be used in rabbits and rodents as in other small animals. The vasoconstrictor epinephrine (1 : 200,000) may be used with topical anesthesia to prolong the local analgesia, which may last up to 4 hours for bupivacaine. Lidocaine at 0.5–1.0% or preservative-free morphine may be used for epidural anesthesia in rabbits. Epidural lidocaine administration to rabbits results in mesenteric venodilation. The total volume of any local anesthetic must be carefully calculated to avoid systemic toxicity in small mammal species, and it may induce sudden cardiovascular collapse if given accidentally by IV injection. Incisional or testicular blocks are also frequently performed in practice.

EMLA® or Maxilene® cream (with active ingredients of prilocaine/lidocaine and lidocaine, respectively) can be used topically (pea-sized amount applied with a cotton-tipped applicator) to desensitize skin for procedures such as venipuncture or ear tagging or tattooing.

Anesthesia in Rabbits

The overall risk of anesthetic-related death in rabbits is 1.39%, with the risk in healthy animals being 0.73%, and in sick animals being 7.37%. This is much higher than the risk in dogs (overall 0.17%; healthy 0.05%; and sick 1.33%) and cats (overall 0.24%; healthy 0.11%; and sick 1.40%). The following concerns make anesthesia of rabbits a challenge: (1) rabbits may be easily stressed and in some cases the physiologic response and catecholamine release are marked (as described); (2) if inadequately restrained, rabbits may struggle during face mask induction and luxate or fracture lumbar vertebrae; (3) rabbits may breath-hold for extensive periods during anesthesia induction; (4) preexisting respiratory disease, such as that caused by infection with *P. multocida*, odontogenic rhinitis, or thymoma, a small, easily occluded trachea, a capacious cecum, and considerable variation between individuals complicate induction and may cause varied responses to anesthetics; (5) unpredictable responses to atropine because of plasma atropine esterase; (6) rabbits have limited coronary vascularization, which predisposes them to myocardial ischemia with coronary vasoconstriction; and (7) dehydration, hypothermia, and postoperative gastrointestinal stasis and inappetence often occur.

With some care and preplanning, and by implementing balanced anesthesia to minimize any undesirable effects of the drugs used, most rabbits are anesthetized safely and without difficulty. While endotracheal intubation requires practice, anesthesia usually presents few real problems, provided animals are not excited or permitted to struggle during induction.

Inhalant Anesthetics in Rabbits

Inhalant anesthetics are very useful in rabbits, assuming appropriate concentrations are delivered, and precautions are followed concerning body warmth and hydration. Preanesthetic

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FIGURE 3.44. Facemask induction of a rabbit.

medication with a tranquilizer or sedative, whenever possible, and analgesic, when indicated, will help minimize stress. Induction can then be accomplished more easily by face mask or IV administration of propofol or alfaxalone (Figure 3.44). Induction can also be carried out with appropriate IM dosages of alfaxalone, ketamine plus a sedative, such as acepromazine, diazepam or midazolam, xylazine, medetomidine, or dexmedetomidine. See Table 3.13 for some suggested drugs and dosages.

Rabbits have a respiratory rate of approximately 30–60 breaths/min and a tidal volume of 4–6 mL/kg, which is small compared with cats at 10–15 mL/kg. Inhalant anesthetics are administered to rabbits via a nonrebreathing circuit using a contoured face mask, LMA, or an endotracheal tube. Suggested levels for isoflurane are 5% for induction and 2–3% for maintenance, and for sevoflurane are 6–8% for induction and 3–6% for maintenance, with appropriate oxygen flow rate depending on the size of rabbit and whether or not it is intubated. Rabbits are prone to isoflurane-induced hypotension, especially when artificially ventilated. Therefore, balanced anesthetic protocols that decrease the isoflurane requirements and the use of vasopressors may be indicated. Dopamine has not been shown to be effective in rabbits. For anesthetic hypotension, norepinephrine at 0.05–0.2 µg/kg/min and boluses of colloids at 5–10 mL/kg may be used. Premedication drugs, and constant rate infusions of fentanyl (5–20 µg/kg/h), ketamine (2–5 µg/kg/h), or lidocaine (50–100 µg/kg/h) decrease the MAC of isoflurane required to maintain anesthesia in rabbits.

Endotracheal Intubation

If using a laryngoscope for intubation, a Wisconsin laryngoscope blade size 1 is appropriate if the body weight is more than 3 kg and size 0 if the weight is less than 3 kg. A 40 mm laryngoscope is suitable for an adult rabbit. The glottis may be desensitized with 0.25 mL of 1% lidocaine applied with a cotton swab or by aerosol. The laryngoscope blade is "walked" over the tongue to the soft palate followed by the stylet (5 French polypropylene urinary catheter) within the tube (infant Cole endotracheal tube of 2–3 mm OD in 1–3 kg rabbits and 3–4 mm OD in heavier rabbits). The stylet is then either introduced through the glottis and used as a guide or removed before the tube is rotated slightly as it gently advances into the trachea. The stylet, if present, is then removed.

Blind intubation is also possible by placing the rabbit in sternal recumbency and extending its neck such that the nose is pointing skyward without lifting the forefeet from the table. A clear endotracheal tube is inserted into the oral cavity, avoiding the molars, and gently positioned near the glottis. Clouding of the lumen on expiration denotes proper positioning and aids with timing of insertion of the tube into the trachea. Intubation attempts should be limited to two or three tries to avoid damage to the delicate laryngeal tissues. Correct placement is confirmed by palpation of one rigid tube in the throat (tube within trachea only), by hearing breath sounds through the tube, or by positive waves on capnography (Figure 3.45). The blind technique requires practice and has several variants, but once mastered is performed easily in most rabbits.

The over-the-endoscope technique of rabbit intubation is one of the most straightforward techniques to master, with practice. A 2.7 mm rigid endoscope fitted through a 3–3.5 mm uncuffed endotracheal tube is used. Once the rabbit is induced, the head is bent backward, the mouth opened, and the combination endoscope–endotracheal tube is advanced to the back of the throat and pushed dorsally against the soft palate to disengage it from the epiglottis. Then, the scope is advanced into the trachea and the tube is pushed forward while the endoscope is removed. In small rabbits (less than 1 kg), another endoscopic technique is used. The endoscope is used to see the glottis, and a plastic urinary catheter or guide wire is introduced through the operating channel and into the trachea. The scope is then removed, and a 2 mm endotracheal tube is fitted over the catheter or guide.

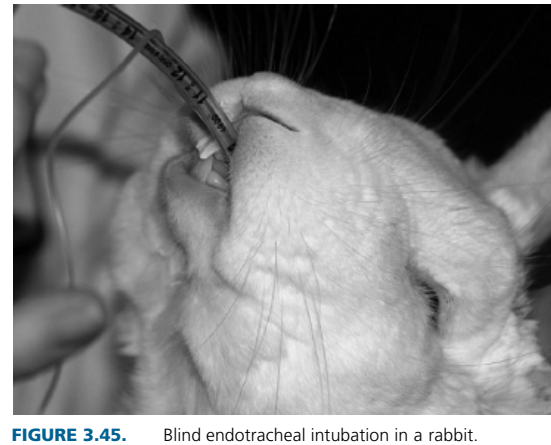


FIGURE 3.45. Blind endotracheal intubation in a rabbit.

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Laryngeal Mask Airways

The LMA is an alternative to a face mask or endotracheal tube and consists of an airway tube, a mask, and a mask inflation link. The mask is inserted over the larynx and forms a junction between the upper airway and the trachea. Insertion of the mask requires some practice to protect it from the rabbit's teeth and to advance it to the correct position, but once in place it provides the ability for positive pressure ventilation (Figure 3.46).

A different supraglottic airway device (laryngeal mask), the V-gel, has been used successfully in rabbits (Figure 3.47). Different sizes must be purchased to accommodate various patient sizes. It is easy to place but must be placed using capnography. Rabbits tend to be more hypercapnic with it than with endotracheal intubation, and the device may get dislodged with head motions. It is a safe and efficient alternative to endotracheal intubation for short or minor procedures.



FIGURE 3.46. Laryngeal mask airway (LMA) (inset) and restraint for LMA placement in the rabbit. Courtesy of A.J. Wang.

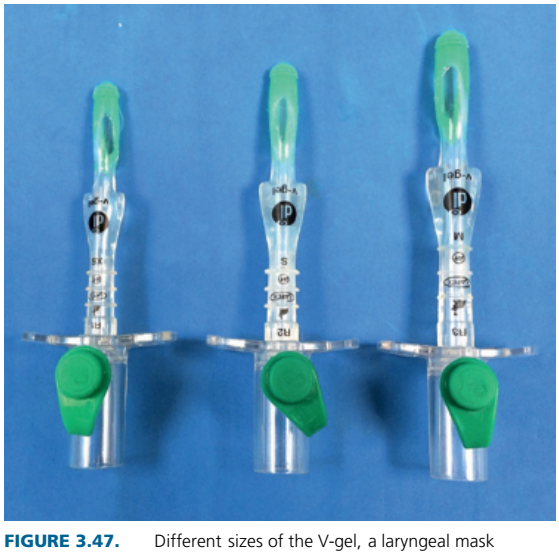


FIGURE 3.47. Different sizes of the V-gel, a laryngeal mask designed for rabbit anesthesia.

Injectable Anesthetic Agents in Rabbits

Injectable anesthetic procedures for rabbits are usually effective, inexpensive, convenient, and simple; however, potential problems with their use include associated respiratory depression, inter-individual variation in depth of anesthesia and analgesia, and difficulty in calculating depth of anesthesia as determined by the various indicator reflexes. The best indicators of depth of anesthesia, in order of decreasing reliability, are ear pinch, pedal withdrawal, corneal (water drop), and palpebral reflexes. The pinna or ear pinch is a sensitive indicator in rabbits and persists longer than do the other reflexes.

Injectable induction agents include alfaxalone, propofol, and ketamine administered either IV alone or IM in combination with one or more drugs with muscle relaxing, sedative, and/or analgesic properties, depending on the intended procedure. Drugs added to or administered with ketamine include acepromazine, xylazine or dexmedetomidine, or diazepam or midazolam. An opioid such as butorphanol, hydromorphone, buprenorphine, or fentanyl may be added for analgesia. Other combinations are outlined in Table 3.14. Supplemental oxygen should always be provided during injectable anesthesia.

Alfaxalone

Alfaxalone produces a dose-dependent sedation in rabbits. It can be administered both IV and IM, either alone, or in combination with another sedative and/or analgesic. Addition of other agents will extend the duration of sedation. A variety of combinations have been reported in the literature, some of which are summarized in the table. Alfaxalone has been license for induction of anesthesia in rabbits via slow IV injection in the United Kingdom since 2017, making it one of few drugs licensed for use in this species.

Ketamine Combinations

Ketamine HCl is a dissociative anesthetic with wide application in rabbits. Ketamine HCl solution is buffered to a pH of 3.5–5.5 and local muscle irritation occurs on injection. Ketamine is rarely given alone as it may induce cardiovascular stimulation, muscle rigidity, salivation, seizures, electroencephalographic changes, and serum chemistry alterations. The popularity of ketamine for use in rabbits is based on mixtures or sequential administration in various combinations with acepromazine, xylazine or medetomidine, diazepam or midazolam, inhalant anesthetics, butorphanol, and other drugs. These combinations may improve muscle relaxation and sedation, augment analgesia, and prolong surgical anesthesia. Some of these combinations are summarized in Tables 3.13 and 3.14.

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Table 3.14. Various CRI protocols for rabbits.

Ketamine/Dexmedetomidine

	Premedication		Induction and Maintenance		
Ketamine	20 mg/kg	IM	300–350 μg/kg/min	CRI	~30 min after premed; 2% topical lidocaine for laryngospasm
Dexmedetomidine	0.125 mg/kg	IM	1.5–1.75 μg/kg/min	CRI	

Lidocaine

	Induction		Maintenance	
Isoflurane	5% in 2 L/min O_2	By mask	isoflurane	ET tube
Lidocaine			2 mg/kg	IV bolus over 5 min
			50–100 μg/kg/min	2 mg/ml CRI after bolus

Propofol

	Induction		Maintenance		
Propofol	4–8 mg/kg	IV	1.2–1.3 mg/kg/min	CRI	
Propofol	12.5 mg/kg	IV	1 mg/kg/min IV	CRI	
Propofol	12.5 mg/kg	IO	1 mg/kg/min IO	CRI	

Ketamine and Xylazine

Xylazine is an alpha-2 adrenergic agonist tranquilizer and potent sedative. Xylazine can be combined with ketamine or administered separately. Ketamine and xylazine are usually combined in a syringe and given IM at 20–50 mg/kg ketamine with 2 mg/kg xylazine, but lower doses of both drugs, especially of xylazine, may be used. Higher dosages of ketamine may be necessary to reach surgical planes of anesthesia, and lower dosages of xylazine may be used to reduce the metabolic alkalosis and increase the arterial oxygen saturation, sensitivity to noise, and profound secondary hypotension that characterize the pharmacologic actions of xylazine. Xylazine also contributes to visceral analgesia and muscle relaxation. The combination may be given by IV infusion as ketamine 1 mg/min with xylazine at 0.1 mg/min or by intranasal instillation of ketamine (10 mg/kg) with 3 mg/kg xylazine diluted with 0.9% saline. Induction for these combinations is approximately 10 minutes, and surgical anesthesia lasts from 10 to 75 minutes (average 30–45 minutes). Supplemental oxygen should always be provided. Recovery from sedation without reversal may take 6 hours. The effects of xylazine may be reversed with an injection of 0.2 mg/kg yohimbine IV or 0.001 mg/kg atipamezole, SC, IV, or IP. A ketamine/xylazine combination given at 50 mg/kg and 5 mg/kg, respectively, has caused severe acidosis, anuria, respiratory depression, and death in rabbits.

Ketamine, Xylazine, and Acepromazine

Ketamine, xylazine, and acepromazine may be used in a three-way mixture (i.e., 35 mg/kg ketamine, 3 mg/kg xylazine, 0.75 mg/kg acepromazine IM) to provide a significantly longer duration of anesthesia (99± 20 minute) than for ketamine/xylazine alone. Side effects include depressed respiratory rate, heart rate, and especially blood pressure (may be critical in a hypovolemic patient). Individual practitioners working with healthy, well-hydrated rabbits may find this combination and the side effects acceptable, especially if IV fluids are provided intraoperatively. Ketamine may be given with acepromazine (1–2 mg/kg IM) alone, without xylazine, for deep sedation, but this combination is not suitable for general anesthesia.

Ketamine and Diazepam

Ketamine at 60–80 mg/kg IM can be preceded by 30 minutes with the benzodiazepine tranquilizer, diazepam, at 5–10 mg/kg IM to provide general anesthesia in the rabbit. The drugs should not be mixed, and diazepam does not potentiate the analgesic effects of ketamine.

Ketamine and Midazolam

Midazolam is a water-soluble benzodiazepine that produces sedation, muscle relaxation, and some respiratory and vascular depression. Ketamine at 15–30 mg/kg mixed with midazolam at 1–3 mg/kg given IM can be used for sedation. These drugs may also be administered intranasally to rabbits in a saline-diluted mixture of 1.0 mg/kg midazolam and 25 mg/kg ketamine. Anesthetic activity persists for approximately 50 minutes.

Ketamine, Medetomidine, and Diazepam

Medetomidine is an alpha-2 adrenergic agonist with sedative and analgesic properties. Medetomidine given at 0.5 mg/kg IM with ketamine (20 mg/kg IM) and diazepam (0.75–1.5 mg/kg SC) provides 7–16 minutes of induction time and 30–60 minutes of surgical anesthesia. Ketamine (25 mg/kg IM) and medetomidine (0.5 mg/kg IM) may also be given without diazepam for surgical anesthesia. Medetomidine should be reversed with atipamezole postoperatively to enhance recovery.

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Ketamine, Xylazine, and Butorphanol

A combination of ketamine 35 mg/kg, xylazine 5 mg/kg, and butorphanol 0.1 mg/kg IM can increase anesthesia time over ketamine/xylazine alone and ensure longer, more predictable analgesia. Less autonomic depression occurs than that associated with a ketamine/xylazine/acepromazine combination.

Propofol

Propofol is an excellent induction agent for rabbits prior to intubation. Recommended IV induction doses range from 5 mg/kg to 15 mg/kg (bolus), but 7.5–8.45 mg/kg is considered the minimum required for intubation, which is much larger than for other companion animals. As for other species, rabbits may become apneic after administration of propofol boluses.

Light anesthesia follows for approximately 2 minutes at 5 mg/kg, 4 minutes at 10 mg/kg, and 9 minutes at 15 mg/kg IV. The slow drip dose is 0.2–0.8 mg/kg/min for sedation and 0.8–1.3 mg/kg/min for anesthetic maintenance. Premedication with acepromazine (2 mg/kg IM), medetomidine (0.25 mg/kg IM), and atropine (0.5 mg/kg IM) may facilitate propofol injections and provide analgesia and muscle relaxation, and this combination reduces the propofol dose to 4 mg/kg IV. Supplementary analgesics should be given if a painful procedure is to be performed, as propofol provides no analgesia. Recovery takes 2–5 minutes and depends on animal weight and not on bolus dose.

Although propofol is safe for rabbits when used and stored properly, it does cause attenuation of the vagal component of heart rate that is under baroreceptor control as well as a 25–30% decrease in cardiac output. Long-term anesthesia with propofol may result in atelectasis, hypoxemia, and hypostatic congestion. Respiratory arrest may occur in rabbits with propofol doses of 20 mg/kg. Propofol does not impair fertility, induces little variation in arterial blood pressures, and does not undergo enterohepatic circulation.

The drug is conjugated in the liver and predominantly (60–90%) eliminated via the kidney, with approximately 2% passing in the feces. The drug can be administered to rabbits via the lateral ear vein.

Hypnorm

Hypnorm is a neuroleptanalgesic combination of a potent narcotic analgesic (fentanyl) and a neuroleptic tranquilizer-sedative (fluanisone) which can be given IM, IP, SC, or IV. It is licensed for use in rats, mice, rabbits, and guinea pigs in the UK. In addition to providing excellent analgesia, the combination suppresses excitement and provides muscle relaxation, especially when combined with a benzodiazepine. Hypnorm is well tolerated in most rabbits, but can produce respiratory depression, hypoxia, and bradycardia. It can be used alone at 0.2–0.5 mL/kg for mild-to-heavy sedation, or mixed with benzodiazepines for surgical anesthesia (see dosages in table). The fentanyl portion can be reversed with 0.5 mg/kg butorphanol or 0.05 mg/kg buprenorphine intravenously, both of which will provide pain relief. In emergencies, naloxone at 0.1 mg/kg IM or IV can be used as a reversal; however, it does not provide any analgesia.

Anesthesia in Guinea Pigs

Healthy, adult guinea pigs have a respiratory rate between 40 and 130 respirations/minute, a heart rate of 240–310 bpm, and an approximate tidal volume of 3.8 mL/kg body weight. The body weight of guinea pigs may be overestimated by the large cecum. The pedal reflex is not always a reliable indicator of a surgical plane of anesthesia in guinea pigs. Postoperative supportive care should include hydration with warmed saline or other fluids, provision of a warm, quiet environment, and special efforts to stimulate postoperative feeding.

Inhalant Anesthesia in Guinea Pigs

Isoflurane

Guinea pigs can be induced using an induction chamber, by face mask (Figure 3.48), or by injection, and maintained on 2–3% isoflurane in oxygen. A small feline anesthetic mask with a nitrile or plastic disposable glove or balloon taped over the opening to construct a diaphragm with an appropriate-sized opening can be used if a commercial guinea pig mask is not available.

Endotracheal Intubation

In guinea pigs, only the rostral 1/3 of the tongue is free and mobile, and a food bolus is often held between the tongue and the hard palate. Before the guinea pig can be intubated, the bolus must be removed. For intubation, the guinea pig is placed in dorsal recumbency, and adhesive tape is used to hold the upper jaw to the table surface. The tongue obscures the larynx in guinea pigs. The mouth is cleaned with nontoxic

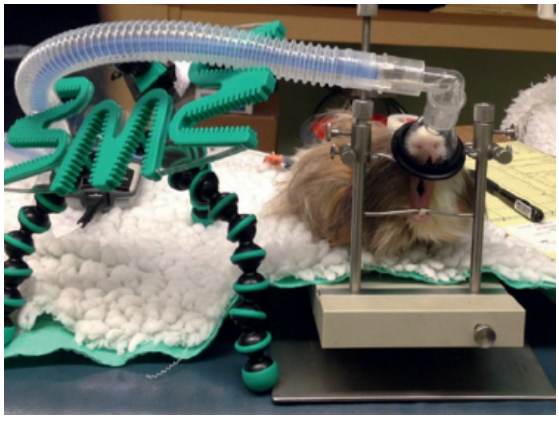


FIGURE 3.48. Mask anesthesia with isoflurane in a guinea pig being prepared for a dental examination.

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organic iodide antiseptic, and an 8 cm, 1.5–2.5 mm OD tube with stylet is passed over a laryngoscope placed to the left of the upper incisors parallel to the floor of the mouth. The tube is introduced to the epiglottis, which is angled upward. Actual insertion into the trachea is conducted blindly during inspiration (Figure 3.49). The tube is passed gently into the trachea, and, if used, a respirator can be set at 25 strokes/min to deliver 1.5 mL/100 g of air/stroke. A mouth gag is placed in the mouth, and the tube is taped to the gag and around the snout.

Endoscopic-guided intubation of guinea pigs is performed as described for small rabbits in sternal recumbency except that when a 2 mm uncuffed endotracheal tube is too large, a 14–16 g IV catheter or a 1–2 mm silicone endotracheal tube may be used instead.

Injectable Anesthetics in Guinea Pigs

It is difficult to achieve surgical anesthesia using injectable agents in the guinea pig, with the exception of Hypnorm (not available in the United States) combined with a benzodiazepine (e.g., midazolam). In addition, intramuscular injections may produce muscle necrosis and self-mutilation, and intraperitoneal injections are inconsistently absorbed. For these reasons, inhalational anesthesia with addition of an appropriate analgesic drug is recommended for major or painful procedures in guinea pigs.

Alfaxalone

Alfaxalone given at 20 mg/kg SC provides about 70 minutes of recumbency and is suitable for non-painful procedures for which complete immobility is not needed. Teeth grinding and twitching may still occur. Alfaxalone alone at 5 mg/kg IM or at 5 mg/kg SC along with midazolam at 0.5 mg/kg SC given in separate syringes also proves good sedation for noninvasive procedures.



FIGURE 3.49. Guinea pig intubated with a 2 mm uncuffed endotracheal tube for an enucleation. Surgery on the head is a strong indication for intubation in rodents.

Fentanyl/Fluanisone (Hypnorm)

Hypnorm is not available in the US, but is licensed for use in guinea pigs in the UK. A dose of 1 mL/kg IM can be used for sedation in guinea pigs; however, it is irritating and can cause post-injection lameness if the entire dose is given in one location. Hypnorm can be combined with a benzodiazepine to produce general anesthesia. Respiratory depression, hypotension, and bradycardia may occur. Diazepam cannot be combined in the same syringe and must be injected separately; however, midazolam is miscible and can be given in the same syringe as the Hypnorm. A dose of 1 mL/kg Hypnorm IP followed by diazepam at 2.5 mg/kg IP can be used. For Hypnorm/midazolam, each drug can be mixed with an equal volume of sterile water first, then the two solutions mixed together in equal volumes. Guinea pigs are dosed at 8 mL/kg of this solution intraperitoneally. Hypnorm may be reversed with the partial opioid agonists, buprenorphine and butorphanol (agonist–antagonist), or with the full antagonist, naloxone.

Ketamine Combinations

Ketamine and Xylazine

Ketamine (40–60 mg/kg) and xylazine (2–5 mg/kg) given IP provide approximately 30 minutes of anesthesia; however, analgesia may not be sufficient for major surgery in some animals and may require the addition of butorphanol. Guinea pigs evince pain on injection, but muscle relaxation is good. IM injection of this combination may produce muscle necrosis and self-mutilation and SC or IP injection may be more suitable.

Acute, fatal gastric distention has been reported after anesthesia of 44- to 49-day pregnant guinea pigs with ketamine at 20 mg/kg and xylazine at 2 mg/kg IM. During the procedure, one external jugular vein was cannulated. Food had not been withheld preoperatively.

Ketamine and Diazepam

This combination may be given as ketamine at 25–100 mg/kg IM and diazepam at 0.1–2.5 mg/kg IM. Pain will occur on injection and the combination provides no analgesia; however, the resulting immobilization may be useful for such procedures as trimming overgrown premolar teeth.

Ketamine and Acepromazine

Ketamine dosages in guinea pigs at 25–55 mg/kg combined with acepromazine at 0.75–3 mg/kg IM, IP, or SC are useful for restraint. This combination provides no analgesia and is not suitable for surgical procedures.

Anesthesia in Chinchillas

The healthy, adult chinchilla has a respiratory rate of 40–80 respirations/min and a heart rate of 100–150 bpm. As with guinea pigs, postoperative care should include hydration with warmed saline or other fluids, provision of a warm, quiet environment, and special efforts to stimulate postoperative

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feeding. Introducing the patient to food treats or other dietary supplements prior to the procedure may facilitate acceptance in the post-operative period.

Isoflurane

Isoflurane is used routinely in chinchillas for the induction and maintenance of general anesthesia. The animal can be induced using an induction chamber (Figure 3.50), by face mask, or by injection, and maintained on 2–3% isoflurane in oxygen. Maintenance is typically continued by face mask due to difficulty with intubation. Small cat masks with an appropriately constructed diaphragm or commercial guinea masks may be used. If intubation is required, it can be performed with the use of an endoscope and a large IV catheter, as described for small rabbits.

Injectable Anesthetics in Chinchillas

Midazolam combined with an opioid, with or without a low dose of ketamine and/or dexmedetomidine is a safe and useful premedication for chinchillas. Injectable anesthetic protocols are sometimes desired to reduce waste-gas exposure, or if inhalant anesthesia is impractical. Ketamine at 4 mg/kg mixed with dexmedetomidine at 0.015 mg/kg and given IM provides effective anesthesia for up to 45 minutes; however, hypoxemia occurs unless supplemental oxygen is provided. Atipamazole at 0.15 mg/kg SC can be used to reverse the dexmedetomidine. Decreased food intake may occur during the post-anesthetic period, so supplemental feeding is indicated, preferably with a substance that has been introduce prior to the procedure, to reduce novel substance aversion. Alfaxalone has not been shown to be useful in chinchillas.

Hypnorm (fentanyl/fluanisone; not available in the US) provides sedation at a dose of 1 mL/kg intramuscularly; however, post-injection lameness may occur due to its irritating nature. Hypnorm can be combined with a benzodiazepine to produce anesthesia, as described above for guinea pigs.



FIGURE 3.50. Chamber induction of a chinchilla.

Anesthesia in Hamsters

Hamsters have a respiratory rate of approximately 35–135 respirations/min, a tidal volume of approximately 0.8 mL, and a minute volume of approximately 64 mL. Depth of anesthesia in hamsters may be determined using righting reflex, pedal withdrawal, and muscle tone, and by pinching abdominal skin with mosquito forceps. The pedal withdrawal reflex is elicited by pinching the interdigital webbing with fingers or forceps for up to 1 s/site.

Inhalant Anesthesia in Hamsters

After induction in a chamber with 5% isoflurane, or by injection, hamsters can be maintained on isoflurane in O_2 at 2–3%, using a tight-fitting rodent face mask or face mask created from a modified 60 mL syringe barrel, taking care to minimize any dead space. Sevoflurane may be used similarly with slightly shorter induction and recovery times.

Injectable Anesthesia in Hamsters

Telazol® and Xylazine

Telazol (tiletamine/zolazepam) at 30 mg/kg combined with xylazine at 10 mg/kg given IP produces approximately 30 minutes of surgical anesthesia. Intramuscular injections of Telazol alone reportedly caused inconsistent anesthesia and muscle necrosis.

Ketamine Combinations

Ketamine and Xylazine

Hamsters may be anesthetized with 50–100 mg/kg ketamine combined with xylazine at 5 mg/kg IP. This dose provided approximately 28 minutes of surgical anesthesia in the extremities and 36 minutes in the abdomen. Intramuscular injection of ketamine causes extensive muscle necrosis in hamsters. Xylazine can be reversed with yohimbine (0.5–1 mg/kg IV, IP) or atipamezole (generally 10× the administered dexmedetomidine dose, SC, IM).

Ketamine and Acepromazine

Ketamine may be given at 100 mg/kg IP with acepromazine at 1–4 mg/kg IM for deep sedation.

Ketamine and Diazepam

Ketamine is given at 100 mg/kg IP with diazepam at 0.5 mg/kg IM or 5.0 mg/kg IP. This combination provides no intraoperative analgesia.

Ketamine and Dexmedetomidine

Ketamine is at 75–100 mg/kg IP with dexmedetomidine at 0.25 mg/kg provides 30–60 minutes of anesthesia. Atipamezole can be used to reverse the dexmedetomidine.

Hypnorm

Hypnorm (fentanyl/fluanisone; not available in the US) combined with either diazepam or midazolam, given IP, provides excellent surgical anesthesia and analgesia lasting about

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20–40 minutes in hamsters. The respiratory depressant effects of the drug can be partially reversed with nalbuphine or butorphanol, while maintaining good postoperative analgesia.

Anesthesia in Gerbils

The respiratory rate of gerbils is approximately 90 respirations/min. As with the other small rodents, after induction in a chamber, or by injection, gerbils can be maintained on isoflurane at 2–3%, using a tight-fitting rodent face mask.

Injectable Anesthesia in Gerbils

Ketamine Combinations

Ketamine (75 mg/kg) and medetomidine (0.5 mg/kg) combined and given SC or IP produces a moderate surgical plane of anesthesia in gerbils. Medetomidine can be reversed using atipamezole (1 mg/kg SC or IP). Ketamine (50 mg/kg) and diazepam (5–10 mg/kg) or xylazine (2 mg/kg) given IP will produce immobilization but not anesthesia, and these combinations are not suitable for surgery. Acepromazine may cause seizures in gerbils and is not recommended.

Fentanyl

A combination of fentanyl (0.05 mg/kg SC) and metomidate (50 mg/kg SC) reliably produces general anesthesia in gerbils. Hypnorm (fentanyl/fluanisone; not available in the US) and a benzodiazepine is reported to be less effective in gerbils than in other rodents, producing only light anesthesia.

Anesthesia in Mice

The mouse has an average respiratory rate of 60–220 respirations/min and an approximate tidal volume of 0.15 mL. Intravenous injections are made using a 28–30 g needle into the lateral tail vein, after restraining the mouse in an appropriate homemade or commercially available device or on the lap for well habituated animals. Warming the tail dilates the vessels and facilitates needle entry. Care should be taken not to inject air emboli.

Inhalant Anesthesia in Mice

As with other small rodents, use of an induction chamber facilitates inhalation anesthesia in mice, after which they can be maintained on isoflurane at 2–3%, using a tight-fitting rodent face mask. Sevoflurane may also be used, with 4.9% reported as 1.5× the MAC in laboratory mice. The MAC of inhalants may vary considerably between mouse strains. Manifolds with multiple ports are commercially available that permit several mice to be anesthetized simultaneously, which may be convenient when batching procedures or surgeries for some research projects. Mice may be intubated for research purposes (Figure 3.51). Anesthesia is not without risk in small mammal pets, and mouse behavior may be altered for many days following general anesthesia with an inhalant agent.

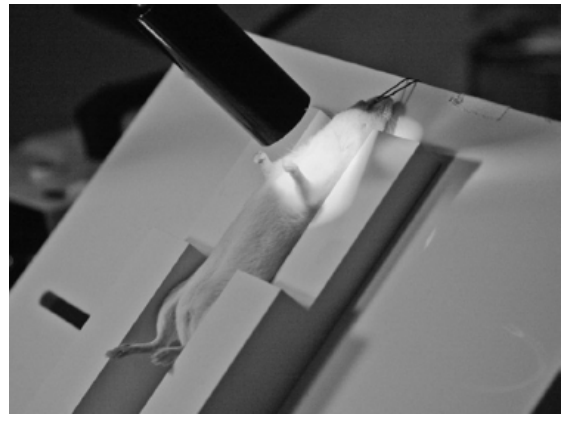


FIGURE 3.51. Mice and rats may be intubated for research purposes. The technique is facilitated with commercially available intubation bases and a bright light source. Identification of the oropharynx is accomplished by shining the light source on the cervical region, as depicted. Courtesy of A.J. Wang.

Injectable Anesthesia in Mice

The response to injectable anesthetic agents is highly dependent on the strain or stock of mouse used. When in doubt, a small pilot study is recommended to optimize the dose levels. It is critical to provide supplemental oxygen and warmth to anesthetized mice to enhance the likelihood of successful post-anesthetic recovery.

Alfaxalone Combinations

Alfaxalone given alone in mice produces a number of undesirable side effects. Doses of 80–100 mg/kg may be suitable for minor, non-invasive procedures; however, popcorn-like jumping, shivering, face-scratching, hyperresponsiveness to noise and leg jerking may occur during induction and recovery. Alfaxalone combinations are variably effective depending on the strain and sex of mouse, and small pilot studies should be carried out to optimize drug dosages.

Alfaxalone and Dexmedetomidine

Alfaxalone at 30 mg/kg plus dexmedetomidine at 0.3 mg/kg, mixed and given IP in transgenic mice on a C57BL/6 background was found to be suitable for lung imaging studies. Atipamezole at 1.0 mg/kg SC was used to reverse the dexmedetomidine.

Alfaxalone, Medetomidine, and Butorphanol

Dosages of alfaxalone at 60 mg/kg in combination with 0.3 mg/kg of medetomidine and 5 mg/kg of butorphanol given SC provide up to 75 minutes of anesthesia which can be reversed with atipamezole. Other combinations include 30 mg/kg of alfaxalone, 0.5 mg/kg of medetomidine, and 5 mg/kg of butorphanol given SC, which provide up to 60 minutes of anesthesia. Thermal support is imperative with these combinations to mitigate hypothermia.

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Alfaxalone and Xylazine

In C57BL/6J mice, dosages of 40–80 mg/kg alfaxalone with 10 mg/kg xylazine in females and 80–120 mg/kg alfaxalone with 10 mg/kg xylazine given IP in males produce surgical anesthesia. Outbred mice may be less sensitive to this combination. In addition, the route of administration and type of surgery being performed greatly affect the success of the procedure. Subcutaneous administration may be preferable in some instances.

Ketamine Combinations

Ketamine combinations administered intraperitoneally or subcutaneously are often used in instances when inhalational anesthesia is not practical. Ketamine (100 mg/kg) and acepromazine (5 mg/kg) or diazepam (5 mg/kg) or midazolam (5 mg/kg) may produce immobilization or light anesthesia in some strains. Ketamine (75 mg/kg) and medetomidine (1.0 mg/kg) given IP produces moderate surgical anesthesia in most strains of mice but may not be suitable for laparotomy. Ketamine (80–100 mg/kg) and xylazine (10 mg/kg) may provide up to 30 minutes of surgical anesthesia, depending on the strain of mouse. A combination of ketamine (80 mg/kg) plus xylazine (8 mg/kg) and acepromazine (1 mg/kg) given IP provides balanced anesthesia and can produce up to 50 minutes of surgical anesthesia depending on the strain of mouse.

Extension of injectable anesthesia by bolus redosing is a common practice but may not always produced the desired effect due to the different half-lives of the drugs used. In addition, the timing of redosing can be tricky as mortalities can occur if additional drugs are given while the animal is still in a surgical plane; however, waiting until the animal begins to recover may subject it to pain and discomfort, depending on the procedure. One practice is to redose IP at 50% of the initial ketamine dose or 25% of the initial combined ketamine–xylazine dose when the pedal withdrawal reflex reappears.

The use of a constant rate infusion of ketamine administered intraperitoneally may be a useful alternative to redosing. Ketamine at 80 mg/kg, xylazine at 8 mg/kg, and acepromazine at 0.1 mg/kg, followed by a constant rate infusion of ketamine at 80 mg/kg/h, have been used to prolong injectable anesthesia more consistently than redosing, as has ketamine at 80 mg/kg, xylazine at 8 mg/kg, and acepromazine at 0.5 mg/kg followed by a constant rate infusion of 40 mg/kg/h ketamine and 4 mg/kg/h xylazine. Provision of thermal support during the anesthetic period is critical to reduce mortalities, as is fluid replacement therapy and post-operative nutritional supplementation when permitted.

Medetomidine

Medetomidine at 0.3 mg/kg combined with 4 mg/kg of midazolam and 5 mg/kg of butorphanol given IP or SC provides surgical anesthesia for up to 40 minutes in various strains of mice, including ICR, BALB/C, and C57BL/6J; however, mice may become very hypothermic. Decreasing the dose of medetomidine to 0.2 mg/kg and increasing the dosages of midazolam and butorphanol to 6 and 10 mg/kg, respectively, provide adequate anesthesia while mitigating the hypothermic effects of the medetomidine. Reversal with atipamezole also assists in post-anesthetic recovery of normothermia.

Fentanyl and Hypnorm

Fentanyl (0.06 mg/kg) and metomidate (60 mg/kg) combined and given SC will produce surgical anesthesia in some mice. Hypnorm (fentanyl/fluanisone) given at 0.01 mL/30 g body weight IP will provide sedation for 30–60 minutes. It can also be combined with a benzodiazepine to provide surgical anesthesia lasting 30–40 minutes, and can be partially reversed with either nalbuphine (1.0 mg/kg SC, IP), butorphanol (2 mg/kg SC, IP), or buprenorphine. Diazepam is given at a dose of 5 mg/kg IP in a separate syringe from the Hypnorm. Midazolam can be mixed in the same syringe as Hypnorm, and a useful combination is to mix each drug individually with an equal volume of sterile water, then to mix these two solutions together in equal volumes to form a stock solution. Mice are dosed at 10 mL/kg IP.

Propofol

In mice, propofol given IV at 26 mg/kg leads to 4–6 minutes of anesthesia. The LD_{50} of propofol in mice is approximately 53 mg/kg.

Tribromoethanol Solutions

Tribromoethanol solutions of tert-amyl alcohol and 2,2,2-tribromoethanol have been used for short-term imaging or surgical procedures in mice, rats, and gerbils. The mixture is popular in research settings because it is not a controlled substance and can be prepared from readily purchased nonpharmaceutical-grade chemicals. The working solution must be prepared in a sterile fashion (i.e., filtered through a 0.2 µm sterile syringe filter), protected from light, and kept refrigerated. The working solution must be pH tested before each use and should not be used if below 7.0. When used, the solution should only be administered on a single occasion in any animal because of the risk for adhesions and ileus with repeated IP use. Because of this, some institutions only permit the mixture to be used during acute terminal procedures in rodents. Tribromoethanol is an irritant, especially at high doses, high concentrations, or with repeated use. Tribromoethanol degrades in the presence of heat or light to produce toxic byproducts, and these degraded solutions can be both nephrotoxic and hepatotoxic. Administration of degraded tribromoethanol solutions has been associated with death, often 24 hours after surgery.

Anesthesia in Rats

The respiratory rate of rats is 70–115 breaths/min, and the tidal volume is 0.6–2.0 mL.

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Inhalant Anesthesia in Rats

Use of an induction chamber with 5% isoflurane facilitates inhalation anesthesia in rats, after which they can be maintained at 2–3%, with an oxygen flow at 0.5–1 L/min using a tight-fitting rodent face mask. As for mice, anesthesia machine manifolds with multiple ports are commercially available that allow several rats to be anesthetized at a time, which may be useful for some research projects. Lack of withdrawal following a toe or tail pinch is the most reliable indicator of appropriate anesthetic depth in rats.

Injectable Anesthesia in Rats

It is critical to provide supplemental oxygen and warmth to anesthetized rats to enhance the likelihood of successful postanesthetic recovery.

Alfaxalone Combinations

As in other species, alfaxalone administered as a sole agent only produces light anesthesia in rats and males appear to require higher dosages than females. A dose of 20 mg/kg IP has been suggested for females. A dose of 30 mg/kg alfaxalone plus 0.05 mg/kg dexmedetomidine administered IP is suitable for surgical anesthesia in female rats.

Alfaxalone Constant Rate Infusion with Ketamine and Xylazine

Alfaxalone at a constant rate infusion of 10 mg/kg/h IV has been shown to be useful for extending the anesthetic period of ketamine and xylazine administered SC at dosages of 80 mg/kg and 8 mg/kg, respectively, for surgical procedures lasting up to 35 minutes.

Ketamine Combinations

Ketamine (75 mg/kg) and xylazine (10 mg/kg) or medetomidine (0.5 mg/kg) mixed together and given SC or IP provides surgical anesthesia in most strains of rats. Light anesthesia can be accomplished with ketamine (75 mg/kg) combined and given IP with acepromazine (2.3 mg/kg), diazepam (5 mg/kg), or midazolam (5 mg/kg). Xylazine and medetomidine mixtures cause profound hypotension and hypoxemia, and supplemental oxygen should always be given. Both drugs can be reversed with atipamezole (1 mg/kg SC). Certain strains such as Wistar, Long–Evans, and Fischer 344 rats may have an increased risk for developing postanesthetic corneal lesions with ketamine–xylazine.

Fentanyl and Hypnorm

Fentanyl (300 µg/kg) and medetomidine (300 µg/kg) mixed and given IP produces approximately 60 minutes of surgical anesthesia in rats. Recovery can be facilitated by reversal of fentanyl with either nalbuphine (1.0 mg/kg SC, IP) or butorphanol (2 mg/kg SC, IP), and reversal of medetomidine with atipamezole (1 mg/kg SC, IP). Hypnorm (fentanyl/fluanisone; not available in North America) given at 0.4 mL/kg body weight IP will provide sedation for 30–60 minutes. It can also be combined with a benzodiazepine to provide surgical anesthesia with excellent muscle relaxation lasting approximately 20–40 minutes. Diazepam is given at a dose of 2.5 mg/kg IP in a separate syringe from Hypnorm at 0.3 mL/kg. Midazolam can be mixed in the same syringe as Hypnorm, and a cocktail can be made by mixing each drug individually with an equal volume of sterile water, then mixing these two solutions together in equal volumes to form a stock solution. Rats are dosed at 2.7 mL/kg as a single intraperitoneal injection. The fentanyl component can be reversed as described above.

Propofol

In rats, propofol may have effects similar to those seen in other species. Induction is stress-free and relaxation may be maintained for up to 3 hours (1–2 mL/kg IV for induction, then constant infusion at 4–6 mL/kg/h to effect). In rats, 60–95% of injected propofol is eliminated in the urine, and 13–31% in the feces. Doses of 5 mg/kg (IV) produce approximately 2–4 minutes of sleeping time, and doses of 25–30 mg/kg produce 15–32 minutes of anesthesia. In rats, no enterohepatic circulation occurs. The LD_{50} of propofol rats is 42 mg/kg.

Endotracheal Intubation of Small Rodents

The trachea can be entered through a tracheostomy or by deep tissue (bright light) illumination of the oropharynx. The standard method, however, is to pass a tube through the mouth and into the glottis. Direct observation of the pharynx and laryngeal areas is important (Figure 3.51). The anesthetized rodent is placed in dorsal recumbency with the head extended and the upper jaw taped to the table top. The tongue is pulled sideways and upward, and an otoscope cone with a slit in one side or a 0.4 mm 10×25 mm curved spatula is placed over the base of the tongue. Alternatively, a penlight placed over the external surface of the neck will permit direct viewing of the trachea during tongue retraction.

Elevation of the tongue reveals the glottis, which can be wiped with 1% lidocaine on a cotton swab. The tube (16 g catheter of 1.0–1.5 mm OD in hamster or mouse, 2.0–2.5 mm OD in rat) should be shortened to reduce dead space and is passed (rotating) into the trachea on inspiration. The end of the tube should be blunted to reduce laryngeal trauma. Proper placement is determined by movement of a hair held over the end of the tube. If used, a respirator is set at 1.5 mL/100 g body weight to deliver 25–80 strokes/min.

Expanded and ongoing use of mice in biomedical research has spawned an explosion of devices available to facilitate this research. Among these are platforms specially designed to facilitate endotracheal intubation in mice. Techniques described for intubating other small rodents may also be applied to mice.

In rats, a simple technique using a custom-made mouth gag with a syringe and IV catheters can be used for intubation (see references). Endoscopic-guided intubation may also be achieved using a 2.7 mm rigid endoscope.

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https://veteriankey.com/small-mammal-handling-and-chemical-restraint/#:~:text=When%20transferred%20from%20one%20room,length%20of%20the%20rabbit's%20body—Small mammal handling and chemical restraintlveterinarian key.

ANALGESIA

The International Association for the Study of Pain defines pain as: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Pain can be further categorized as acute, chronic, or visceral. Acute pain may result from an injury or surgical wound, while visceral pain results from the activation of stretch or pressure receptors in visceral organs. Unalleviated or poorly treated acute pain can progress to chronic pain.

There are moral, legal, and ethical obligations to provide appropriate pain management to animals. Principles of appropriate pain management go hand in hand with successful anesthesia techniques. For both human and veterinary medicine, successful analgesia therapy is achieved by preemptive and multimodal treatment. This avoids the physiologic phenomenon known as wind-up, in which chronic, unrelieved pain induces a hyperalgesic state that is much more difficult to relieve. Knowledge and understanding of animal pain have increased dramatically in recent years, and the use of analgesics in research and companion rabbits and rodents is considered a moral imperative and ethical responsibility of the clinician and researcher. Analgesics accompanied by competent nursing care are essential to complete perioperative care of the patient, but do not substitute for good surgical technique.

Analgesics are selected for potency and duration of effect and also with an eye to their potential side effects. For research animals, some consideration should also be given to their potential for interference with the research project, although requests to eliminate analgesic use for painful procedures should be challenged. Some analgesia side effects include heightened activity, pica, sensitivity to noise, cardiovascular or respiratory system depression, decreased gastrointestinal motility, reduced water or food consumption, interactions with other drugs, and alterations in basal physiologic characteristics. Contemporary literature reviews continue to suggest that insufficient analgesia is provided for research animals following painful procedures.

Analgesics should always be given for procedures or conditions that might be considered painful when conducted in humans. As a rule of thumb, the duration of analgesia supplied should be at least 12–24 hours for minor or superficial surgery (e.g., skin biopsy), up to 72 hours for major surgery (e.g., ovariohysterectomy), and up to 1 week for major orthopedic or intrathoracic surgical procedures. While these generalizations may be useful for periprocedural planning, individual animals should always be monitored closely for evidence of pain behaviors and treated accordingly (Figure 3.52).

Pain may be very difficult to detect in rabbits and rodents because they are prey species and instinctively hide behaviors that may be detrimental to their overall survival if noted by potential predators. Physiological, behavioral, and physical

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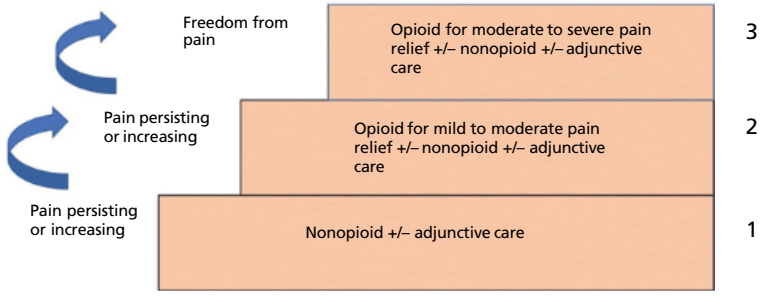


FIGURE 3.52. The World Health Organization's (WHO's) Pain Relief Ladder for Patient Management (Adapted from https://www.who.int/cancer/palliative/painladder/en). This ladder models an approach for the veterinary clinician, Institutional Animal Care and Use Committee (IACUC), and research team to use for pain management in laboratory rodents, based on the anticipated level of invasiveness of procedures being conducted. For example, for a short recovery procedure, such as jugular vein cannulation being conducted by a skilled surgeon, the animal may require peri-operative NSAID treatment in addition to excellent postoperative nursing care. In all cases, regardless of the approved protocol, each patient should be assessed after the procedure to ensure that pain is being well managed. In the event that an animal appears uncomfortable, an escalation to the next higher level of care in the pain ladder should be considered. Reprinted with permission from AALAS Foley et al., (2019).

parameters have all been used to develop different scoring systems to assess pain in these animals. Typical pain manifestations in rabbits and rodents include decreased food and water intake, weight loss, piloerection, listlessness, salivation, chromodacryorrhea, chewing, licking, tooth grinding (bruxism), hunched posture, vocalization, self-mutilation, or aggression. Facial grimace scoring, which is commonly used to assess pain in infants and non-verbal human patients, has been developed for rabbits, mice, rats, and other research animals, and are referred to as grimace scales. Scoring of specific parameters, such as orbital tightening, nose bulging, and ear position, is used to measure pain severity (see Chapter 4). Grimace scales should be used in concert with other parameters, such as body posture and behavior, to assess pain as they may be inappropriate to apply to every individual animal in every situation. Continued identification of typical species behaviors that are altered by pain and can be restored by analgesia will assist in better understanding pain response and alleviation. Assessment tools that use remote technology, such as home cage ethogram analysis, automated facial grimace analysis, and smart cage read-outs of animal physiology and activity, can provide unobtrusive and more accurate monitoring of pain.

The general classes of drugs used to relieve pain include nonsteroidal anti-inflammatory drugs (NSAIDs), opiates and opioids (synthetic narcotic derivatives), and locally acting agents (e.g., topical and local anesthetics, as described in the previous section). NSAIDs are generally short-acting drugs, but they provide significant anti-inflammatory and analgesic action, for example, ketoprofen and meloxicam. Opiates and opioids provide a short-to-moderate duration of action and mild-to-moderate analgesia with the exception of full mu-receptor opioid agonists, which provide high levels of analgesia, for example, morphine, oxymorphone, and fentanyl. The choice of agent is dependent on the patient status and the procedure, but in general, a combination of agents with different noncompetitive pharmacologic actions provides the best analgesic coverage. Analgesic dosages compiled from a variety of sources are listed in Tables 3.15 and 3.16.

Opiates and Opioids

Opiates (plant-derived alkaloids) and opioids (synthetic) commonly used in rabbits and rodents include buprenorphine, hydromorphone, butorphanol, fentanyl, morphine, and tramadol.

Buprenorphine hydrochloride is a partial mu-agonist, delta- and kappa-antagonist, and nociception receptor agonist used primarily for its analgesic effects. It can also be used to reverse the depressant effects of full mu-opioids, such as fentanyl or morphine, while still providing postprocedural analgesia. Because of its slow onset of action, the drug should be given early in the procedure. Side effects include mild respiratory depression that is not readily reversed by naloxone, and pica, which is particularly evident in rats at higher doses. Buprenorphine may increase postoperative activity, decrease food intake leading to body weight loss, and alter circadian rhythm. The increased activity caused by this analgesic may disguise the behavioral effects of pain itself. Adequate water consumption is a good indicator of the intended analgesic effect of the drug. Buprenorphine is useful because of its extended duration of action, which may be 6–8 hours. Simbadol®, a high-concentration formulation of buprenorphine, results in longer duration analgesia of up to 24 hours. However, Simbadol has been associated with adverse neurologic side effects in rabbits. Ethiqa XR is a pharmaceutical grade, FDA-indexed extended-release buprenorphine formulation indicated for the control of postprocedural pain in mice and rats for up to 72 hours. Ethiqa XR must only be given subcutaneously.

Butorphanol tartrate is a mu-agonist/kappa-antagonist opioid analgesic and can also be used to reverse the effects of mu-opiates and still provide analgesia. It has minimal cardiovascular

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Table 3.15. Suggested analgesic dosages for rabbits, guinea pigs, and chinchillas. (Caution: most uses and dosages are extralabel.)

Drug	Rabbit (mg/kg)	Guinea Pig (mg/kg)	Chinchilla (mg/kg)
NSAIDS			
Acetylsalicylic acid	10–100 PO q8–24 h	50–100 PO q4h PO	87 PO
Carprofen	1–2.2 PO q12h	1–2 PO q12–24 h 4 SC q24h	4 PO q24h
Flunixin	1.1 SC,IM q12h	2.5–5.0 SC q12–24 h	1–3 SC q12h
Ketoprofen	1 IM q12–24 h	1–2 SC. IM q12–24 h	1 SC q12–24 h
Meloxicam	1 PO,SC q 24 h 0.5 PO,SC q12h	0.1–0.3 PO,SC q24h	0.1–0.3 PO,SC q24h
Piroxicam	0.2 PO tid	6 PO q24h	
Opioids			
Buprenorphine	0.01–0.05 SC,IM,IV q6–12 h	0.1–0.2 SC, q8–12 h	0.1–0.2 SC, q8–12 h
Buprenorphine (high concentration, Simbadol)	0.24 SC mg/kg q24h		
Butorphanol	0.1–1.0 SC,IM,IV q4–6 h	0.4–2.0 SC q4h	0.2–2.0 IM q4h
Meperidine	5–10 SC,IM q2–3 h	2–10 SC,IM q2–3 h	10–20 SC,IM q6h
Morphine	2–5 SC,IM q2–4 h	2–5 SC q4h	2–5 SC; q2–4 h
Hydromorphone	0.1–0.2 SC,IM,IV q6–8 h	0.1–0.3 SC,IM,IV q6–8 h	0.1–0.2 SC,IM,IV q6–8 h 2 mg/kg SC
Oxymorphone	0.05–0.20 SC,IM q6–12 h	0.2–0.5 SC q6–12 h	
Fentanyl patch (Duragesic)	0.5 patch per 3 kg rabbit × 72 h		
Fentanyl (CRI)	2–10 µg/kg/h	2–10 µg/kg/h	2–10 µg/kg/h
Tramadol	5–10 PO q8-12h (low plasma concentrations) 5 IV,SC		Not effective; do not use
Local Anesthetics			
Bupivacaine	<1.5 infiltrated SC		
Lidocaine	<2 infiltrated SC		
Others			
Ketamine (CRI)	0.2–2 mg/kg/h		
Lidocaine (CRI)	30–100 µg/kg/min (also gastrokinetic effects)		
Other			
Gabapentin	3–5 PO q12–24 h	3–5 PO q12–24 h	3–5 PO q12–24 h

effects and produces mild respiratory depression. Butorphanol tartrate causes decreased food intake. The duration of effect is 2–4hours with a half-life in rabbits of 3.16 hours after SC injection, and the drug is more suitable for acute rather than chronic pain. Butorphanol significantly reduces the MAC of isoflurane in rabbits such that lower inhalant levels are needed to maintain general anesthesia, improving the safety of the anesthetic procedure when both agents are used together.

Hydromorphone is a semisynthetic opiate related to morphine that has mu-opioid receptor agonist activity. Hydromorphone is approximately five times more potent than morphine, with reported onset times between 15 and 30 minutes in mammals, depending on the route of administration.

Fentanyl is a mu-opiate with a rapid onset of action, and it produces profound analgesia, sedation, and respiratory depression. It can be antagonized by butorphanol and buprenorphine. The duration of action is very short, only 30–60 minutes. A slow-release transdermal patch (12 µg/h), lasting up to 48 hours, is also available and has been used in rabbits. The patch must be protected from oral ingestion and must be placed on clipped skin 24 hours prior to induction of a painful procedure.

Morphine is a mu-opiate agonist and produces marked sedation in addition to analgesia. The duration of effect is approximately 4 hours. Oxymorphone is considered a more potent opiate than its parent compound, morphine.

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Table 3.16. Suggested analgesic dosages for hamsters, gerbils, mice, and rats. (Caution: most uses and dosages are extralabel. All dosages listed are mg/kg).

Drug	Hamster	Gerbil	Mouse	Rat
NSAIDS				
Carprofen	5 SC q24h	5 SC q24h	5 SC,PO q24h	5 SC,PO q24h
Flunixin	2.5 SC q12–24 h	2.5 SC,IM; q12h	2.5 SC q12–24 h	2.5 SC q12–24 h
Ketoprophen	5 SC	5 SC	5 SC	5 SC
Meloxicam			1–2 PO,SC	1.0 PO,SC; q24h
Piroxicam	3 PO; q24h	3 PO; q24h	3 PO; q24h	3 PO; q24h
Opioids				
Buprenorphine HCl	0.1–0.5 SC q8h	0.01–0.2, SC, IM; bid-tid	0.05–2.5 SC q6–12h	0.02–0.50 SC,IM,IP,IV q6–12h OR 0.10–0.25 PO q8–12h
Ethiqa XR (extended release buprenorphine)		1 SC	3.25 SC; may be repeated once after 72 h	0.65 SC; may be repeated once after 72 h
Butorphanol	1–5 SC q4h	1–5 SC; q2–4h	1–5 SC q4h	1–2 SC q4h
Hydromorphone	0.05–0.2 SC, IM, IV q6-8h			0.4 SC < q2h
Meperidine	20 SC q2–3h		10–20 SC q2–3h	10–20 SC q2–3h
Morphine	2–5 SC q2–4h	2–5 SC; q2–4h	2–5 SC q2–4h	2–5 SC; q2–4h
Oxymorphone	0.2–0.5 SC q6–12h	0.2–0.5 SC,IM; q6–12h	0.2–0.5 SC q6–12h	0.2–0.5 SC q6–12h
Tramadol				40 PO q24h
Other				
Gabapentin	50 PO q24h		10–30 PO	30 PO q8h

The duration of effect is 2–4 hours. Respiratory depression and bradycardia may occur with its use, and adverse effects can be reversed with naloxone.

Nalbuphine is a mixed agonist/antagonist used as an analgesic and also to reverse effects of mu-opioids. The duration of effect is approximately 4 hours. Pentazocine is a mixed opioid agonist/antagonist. It has a rapid onset of action and will reverse the effects of mu-opioids. The duration of effect is 3–4 hours.

Naloxone is a pure antagonist to the opiate/opioid agonist-antagonists listed above. A dose of 0.01–0.1 mg/kg reverses sedative and depressant effects of these analgesics. Naloxone has a duration of action of 45–90 minutes and may need to be readministered, if the duration of action of the original opiate or opioid exceeds this time period.

Tramadol is a synthetic opioid with low activity at the mu opioid receptor that is used to treat mild acute and chronic pain due to osteoarthritis and neoplasia. It is a controlled substance in both the US and Canada. It can be given orally, and it is relatively inexpensive compared to other opioids. Tramadol is highly unpalatable, and a strong flavoring agent should be used to maximize acceptance of the drug. Tramadol has minimal effects on gastrointestinal motility in rabbits.

Nonsteroidal Antiinflammatory Drugs

NSAIDs (e.g., flunixin, ketoprofen, carprofen, meloxicam) are useful analgesics for mild-to-moderate pain, when inflammation is present, or in situations where opioids are contraindicated. They may also be administered together with an opioid to provide synergistic and balanced analgesia. Most formulations do not provide more than 4–6 hours of pain relief for rodents and rabbits, and because most are cleared by renal mechanisms, animals must be well hydrated throughout NSAID therapy. Chronic administration, e.g., for dental pain in rabbits, may lead to reduced renal function, which should be discussed with the client. The quality-of-life advantages generally outweigh concerns for quantity of life.

Flunixin meglumine is not recommended for use in rabbits because of uncertain analgesic properties when used in that species. For some of these compounds, oral formulations are not available, and tablets must be crushed and mixed with flavored syrup and given slowly through a syringe at the corner of the mouth. One exception is the liquid suspension formulation of meloxicam, which can readily be given by mouth and has the added benefit of lasting up to 24 hours. Meloxicam administered as 10 mg/kg SC q12h in mice provides moderate analgesia, whereas carprofen provided at 10 or 20 mg/kg SC did not provide any analgesia in female mice.

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SURGERY

Many indications for and general admonitions regarding surgery of rabbits and rodents exist. Rodents are small, which necessitates special instruments and skills. They lose body heat and fluids rapidly, and surgical anesthesia is not always easily obtained, especially for long procedures. Preoperative stabilization, asepsis, hemostasis, corneal protection, pain relief, prevention of hypothermia, and postoperative care remain essential concerns and responsibilities (see Supportive Care section under Anesthesia). Fluid replacement should be provided with isotonic fluids before and during the procedure. Apparently small blood losses may have serious consequences, for example, 20% of total blood volumes (TBV) are as follows: mouse 0.4–0.6 mL (8–12 drops); gerbil 1.0–2.0 mL; hamster 1.0–2.4 mL; rat 4–6 mL; guinea pig 8–16 mL; chinchilla 6–10 mL; and rabbit 65 mL. Because rabbits and rodents do not vomit, withholding feed for long periods prior to surgery is not necessary, as it may lead to postoperative ketoacidosis. For rabbits, guinea pigs, and chinchillas, 4–6 hours of food withdrawal will reduce ingesta content, provide a more accurate body weight for drug dose calculations, and decrease the amount of food in the oral cavity. Water should be given up to the time of surgery. A sterile nonmedicated ophthalmic ointment should always be placed on the corneas to prevent drying and ulceration. Temporary tarsorrhaphy may be performed in rabbits with medical tape to decrease the likelihood of post-operative corneal ulcers.

Instruments used for surgery in small animals are suitable for use in rabbits. Additional instruments that may be useful for routine rabbit and rodent surgery include (1) magnification loupes; (2) radio-surgical, electrosurgical equipment, or vessel-sealing devices equipment for hemostasis; (3) automatic skin stapling devices and metal skin clips (9 and 12 mm); (4) sterile cotton-tipped applicators and small pieces of gauze; and (5) other small or microsurgical instruments including iris scissors, small retractors, metal spoons, scalpels, hemostats, burrs, and various small tissue and hemostatic forceps and clips. Perioperative management of rabbits and rodents is covered in Chapter 4.

Surgery in the Rabbit

Surgery in rabbits is often undertaken, both in clinical practice and for experimental purposes. Several procedures are common, including surgery of the reproductive system, urolith removal, orofacial surgeries such as abscess debridement and rhinotomy, and wound repair, ocular procedures, ear surgery, and fracture fixation.

Operative site preparation should be done gently. Care must be taken when clipping fur to prevent abrading or lacerating the thin skin. Rabbit fur is fine and dense, which can make preoperative clipping especially difficult. The hair should be clean and dry, and a clean, sharp no. 40 clipper blade held flat against the skin, as the skin is stretched taut. Clipping itself should be done slowly and carefully to avoid injury. Excessive use of alcohol or wetting of the fur contributes to hypothermia and should be avoided, as should vigorous scrubbing of the fragile skin.

Positioning with head and neck extended helps keep the airway open. Obstruction can occur if the neck is flexed or twisted, even with an endotracheal tube in place. Rabbits are especially susceptible to the complications of dehydration (blood and fluid loss), core temperature depression, hypovolemic shock, ileus, renal and respiratory depression, and postsurgical anorexia. Supportive care should be provided during anesthesia, as discussed previously in the "Anesthesia" section. An intravenous catheter can be placed in the cephalic, lateral saphenous, jugular, or marginal ear veins; or an intraosseous catheter placed for administration of warm replacement fluids at 5–10 mL/kg/h and to provide cardiovascular support and emergency IV access. A catheter placed in the central auricular artery may be used for direct blood pressure monitoring (see Figure 3.37).

Gentle intraoperative tissue handling will reduce postoperative inflammation and associated pain. The skin should be

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closed with a subcuticular pattern, if possible, and the knot buried. Skin sutures may be tolerated if not placed too tightly; however, rabbits often remove skin sutures during normal grooming. Skin staples are more difficult, but not impossible, for rabbits to remove. If used, these should be removed within 7–10 days of surgery. Although convenient for the surgeon, sterile cyanoacrylate skin adhesive should be used with caution in small mammal species, as it induces a strong exothermic reaction that can produce significant skin necrosis, which may impair wound healing. Use of Elizabethan collars is discouraged unless absolutely necessary, as they are not well tolerated and can result in anorexia and further complications. Preoperative habituation to the collar may help to increase tolerance if collar use is deemed absolutely necessary.

Postoperative maintenance fluids should be given at 40–80 mL/kg/d until it is certain the rabbit is eating and drinking sufficiently. If necessary, nutritional support can be provided by syringe-feeding or placement of a nasogastric tube (see "Other Special Techniques" below). Palatable food should be offered in an easily accessible manner to encourage early return to eating and to reduce the risk of postoperative ileus. In patients susceptible to gastrointestinal ileus, a lidocaine CRI (50–100 µg/kg/min) may be continued for a day after the surgery. Post-operative pain management may include SC opioid, oral or injectable NSAID, and CRI of fentanyl and/or lidocaine, as appropriate.

Laparotomy

Before the abdominal wall is incised, the urinary bladder should be emptied by catheterization or by applying gentle manual pressure dorsocaudally on the lower abdomen. Care must be taken, as this thin-walled structure is easily traumatized. A midline incision through the linea alba is appropriate for most abdominal procedures. The urinary bladder and the large thin-walled cecum, which often lie directly beneath the incision, must be avoided on entry.

Rabbits are prone to abdominal adhesion formation and are used as experimental models of postsurgical adhesions in humans. Any foreign material, such as glove talc, lint from cotton swabs, or suture material, may induce adhesion formation. Absorbable, small diameter (4–0 or 5–0), synthetic suture material on an atraumatic needle will help minimize this problem, as will gentle tissue handling and frequent moistening of the viscera with saline. Use of the calcium channel blocker verapamil hydrochloride, 200 µg/kg PO every 8 hours for nine doses, has reduced adhesion formation experimentally and can be used in cases where adhesions are more likely, such as surgery on the bowel, ruptured pyometra, or abdominal abscess. Oral NSAIDS may also help minimize adhesions. Metal hemostatic clips are useful, as they cause minimal tissue reaction, are less likely to tear friable tissue, and reduce surgical time. Catgut and silk are not recommended as routinely used suture materials in rabbits or rodents because of the marked inflammatory response that they induce, which may result in adhesions. The use of the Ligasure® vessel-sealing system may also considerably shorten surgery time, but is expensive.

The peritoneum and muscle layers are usually closed in a single layer, using 3–0 or 4–0 synthetic suture material in a simple continuous or simple interrupted pattern. Care must be taken to oppose, but not crush, the abdominal wall, as tight sutures and ischemia of the peritoneum have been associated with adhesions. The skin should be closed using a subcuticular pattern, taking care to bury the knots. One or two stay skin sutures may be necessary to oppose the skin edges; these likely will be removed by the rabbit overnight but may prevent access to the underlying knot and suture material in the immediate postoperative period. Wound contraction begins the second day post incision and contracts to 40% of the original area by 7 days following surgery.

Ovariohysterectomy

Ovariohysterectomy of companion rabbits is a routine procedure in many veterinary practices and is indicated for both prevention and treatment of a number of disorders. If performed between 5 and 6 months of age, the procedure not only prevents unwanted pregnancy but will prevent uterine adenocarcinoma later in life and may prevent aggression, territorial behavior, and marking. Ovariohysterectomy may also be performed as a treatment for pyometra, reproductive tract neoplasias, venous endometrial aneurysms, or other diseases, and to terminate an unwanted pregnancy.

The reproductive tract of rabbits consists of a long, distensible vagina that leads to a bicornuate uterus, with each horn having its own cervix; there is no uterine body. A marked constriction in diameter delineates each uterine horn from the long, convoluted, friable oviducts. The ovaries are often surrounded by fat and may be difficult to see. The broad ligaments are fat laden and friable, especially in older does. The extremely long gastrointestinal tract of this herbivore completely fills the abdominal cavity and results in constant pressure on the abdominal wall, which must be taken into consideration when incising into and closing the body cavity.

Expression of the urinary bladder should be done gently to avoid trauma or rupture, and is best done with the rabbit held upright, to allow the urine to drain out of the vestibule. Expression of the urinary bladder in dorsal recumbency may allow the urine to pool in the cranial vagina, and possibly leak into the surgical site upon removal of the uterine horns. With the animal in dorsal recumbency, the surgical site is prepared from vulva to midthorax. A 3–5 cm midline incision is made midway between the pubis and umbilicus. The abdominal muscle wall is lifted away from the underlying viscera prior to incising the linea alba, to avoid incising the underlying thin-walled cecum and urinary bladder, which are often pressing against the body wall. Incidentally, pinworms, if present, may be seen clearly through the cecal wall. Intraabdominal fat may obscure vessels, and it increases friability of tissues. The uterus lies dorsal to and often is concealed by the urinary bladder, which should be retracted caudally. After exteriorizing the

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uterus, the ovaries are located at the end of each long, curled oviduct. The ovarian pedicles are fatty and friable, and care must be taken during manipulation and when applying hemostats to prevent tearing. Often there is only room to apply one hemostat. A spay hook should not be used for exposing the ovaries. Ligatures or metal vascular clips are placed, and the stumps transected and inspected for bleeding prior to releasing them. Aternatively a Ligasure forceps can be used to grasp and transect the ovarian pedicle without using hemostats or sutures. Larger vessels of the broad ligament are ligated or cauterized prior to transection. Smaller vessels may be clamped and torn with hemostats. The uterine horns may be transfixed and transected either cranial or caudal to the cervices. Care must be taken to avoid incorporating the ureters. If the uterus is transected caudal to the cervices, the flaccid vagina should be oversewn to prevent leakage of urine into the abdomen. Abdominal wall closure is routine.

Cystotomy

Cystotomy is performed in the rabbit to treat urolithiasis or neoplasia or to thoroughly flush crystals from the urinary bladder to correct urine scalding, if flushing via a urethral catheter has failed. The urinary bladder wall may become grossly thickened due to irritation or infection. Urolithiasis frequently recurs, as the pathogenesis is not completely understood. Associated cystitis should be treated based on culture and sensitivity of urine and a piece of urinary bladder wall. Calcium carbonate calculi are the most common.

A urethral catheter is preplaced to assist with flushing. After routine preparation and incision of the abdominal wall from pubis to umbilicus, the urinary bladder is exteriorized and the surrounding abdomen is packed with moist gauze. Urine is removed from the bladder by cystocentesis. Stay sutures of 3–0 synthetic material are placed at either end of the intended incision and the bladder wall incised, taking care to avoid the ureters and major blood vessels. The urolith or neoplasm is removed, and the urinary bladder and ureters are thoroughly explored, prior to lavaging with copious amounts of warm saline. Saline is flushed through the urethral catheter to dislodge any crystals or calculi, and to ensure patency. A urinary catheter may also be placed from the bladder out the urethra opening, and the urethra is flushed normograde to confirm patency and the absence of further calculi. The bladder wall is closed with a single-layer inverting pattern that does not penetrate the lumen. Abdominal wall closure is routine. Fluids and urethral catheterization may need to be continued for several days postoperatively until the rabbit is urinating freely on its own. The calculus should be submitted for analysis. The calculus, a bladder wall biopsy, or urine should be submitted for bacterial culture.

Gastrotomy

Gastrotomy in the rabbit is indicated for acute gastric obstruction, removal of foreign bodies, treatment of neoplasia, and trichobezoar removal when supportive medical treatment has not been successful or there is clear indication of an obstruction (hyperglycemia, metabolic alkalosis, severe gastric enlargement). Rabbits should be stabilized before surgery with parenteral fluids and analgesics. Post-operative complications and death are common with this surgery in sick rabbits. The abdominal wall is surgically prepared from pubis to midthorax, and a midline incision made, taking care not to damage the underlying organs. Stay sutures are placed in the greater curvature of the stomach, and the surrounding abdomen packed with moist laparotomy pads to minimize contamination. An avascular area of the stomach wall is incised between the greater and lesser curvature. The gastric content is removed using forceps or a spoon, the stomach lavaged with warm saline, and the mucosa examined for ulceration. The pylorus is palpated and probed to confirm patency, and the duodenum is closely examined for viability. Necrotic areas are resected, if necessary. The stomach is closed in a two-layer inverting suture using 3–0 synthetic monofilament. After lavaging the abdominal cavity with warm saline and changing gloves and surgical instruments, closure is routine. Good postoperative nursing care, including fluids, analgesics, supplemental feeding, gut-motility enhancers, and visits from the owner, will hasten recovery.

Other Soft Tissue Surgery

Orchidectomy

Rabbits are castrated to avoid pregnancies; stop urine spraying; reduce aggression; treat orchitis, trauma, or neoplasia; or as part of an experimental study. Rabbits have large, elongated testes, which descend into the scrotal sacs at approximately 2–3 months of age. Inguinal canals remain open throughout the animal's life, and testes move freely between abdomen and scrotal sacs. Intestinal herniation, however, is rare in intact animals because large epididymal fat pads block the passages. Herniation is rare also in castrated rabbits even if the tunics are left open, despite the open passage. Despite this, closed castration, or closure of the vaginal tunic after open castration, is recommended.

The surgical approach may be scrotal or prescrotal. The rabbit is placed in dorsal recumbency, and the scrotal sacs, caudal abdomen, and medial thighs surgically prepared. Gentle abdominal pressure can be applied to push the testicles into the scrotal sacs, if they have been retracted.

The scrotal approach involves making two incisions, one over each scrotal sac. The testicle is stabilized between thumb and forefinger, ensuring that it doesn't inadvertently get pushed back into the abdomen, and a 1 cm incision is made through just the skin, for a closed technique, or through both the skin and the parietal vaginal tunic for an open castration. In a closed castration, the tightly adherent skin is dissected away from the tunic to free up the testicle, and a hemostat applied to the tunic-encased spermatic cord. A transfixing ligature is placed, and the tunic and cord transected distal to the suture and removed (Figure 3.53). In an open castration,

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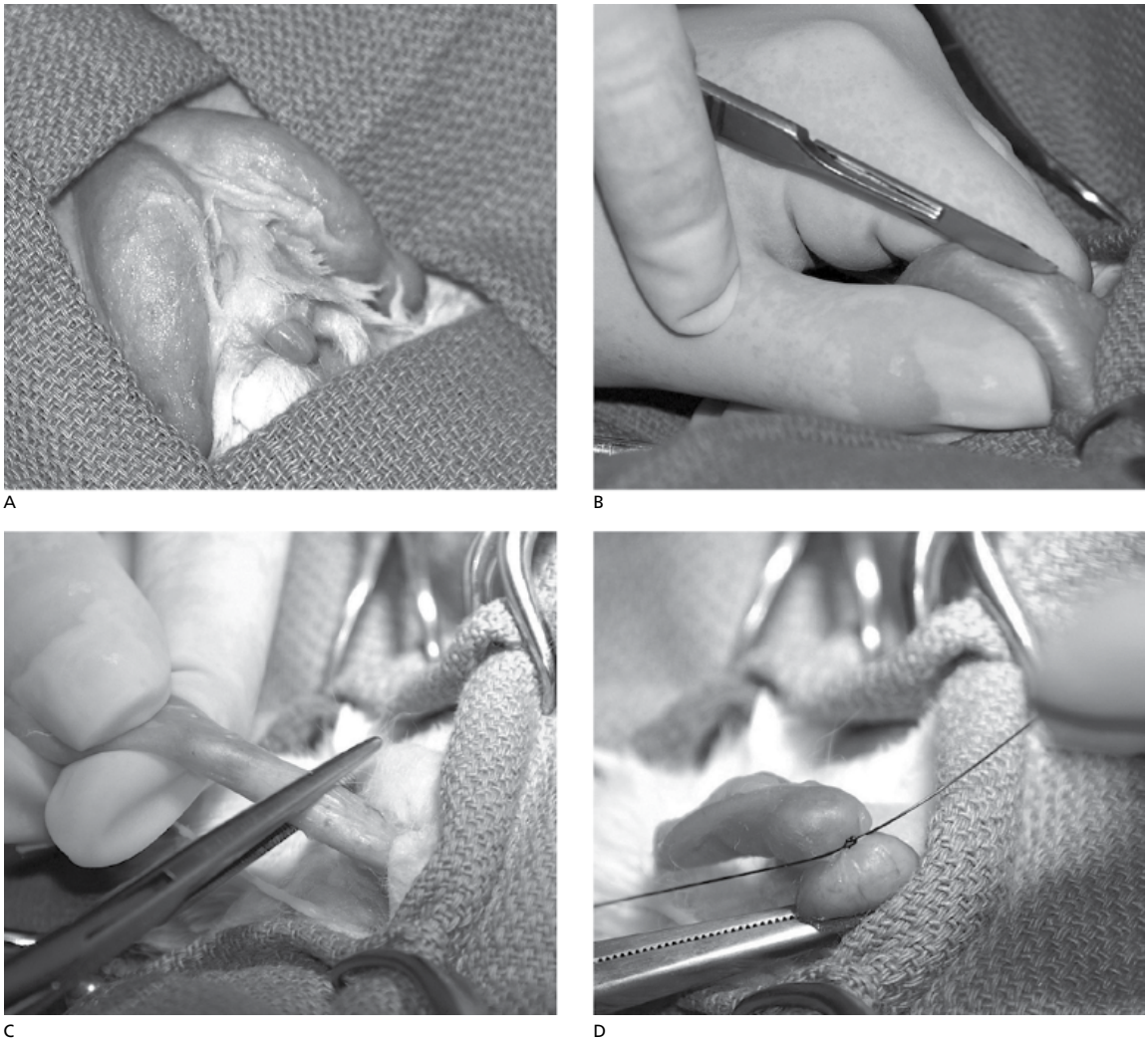


FIGURE 3.53. Technique for closed castration of the rabbit. A: the surgical site is prepped and draped for surgery. B: The skin is incised over the testicle. C: The testicle is exteriorized and the spermatic cord and vessels within the vaginal tunic are clamped. D: The spermatic cord and vessels are ligated, the testicle is removed, and the stump is evaluated for bleeding prior to replacement within the scrotum.

the testicle is exteriorized through the incision in the parietal vaginal tunic, and the spermatic vessels ligated. The gubernaculum is left attached to the lumen of the vaginal tunic, and tension applied to the testicle, which everts the tunic and allows a transfixing ligature to be placed around the tunic as close as possible to the inguinal opening, after which the tunic is transected, in essence removing the same tissues as in the closed technique. Alternatively, the gubernaculum testis is bluntly dissected away from the testicle and the spermatic cord and associated vessels ligated, then the vaginal tunic is closed using a continuous suture pattern. The scrotum is closed with 5–0 nonabsorbable skin sutures or tissue glue, which are usually left alone by the rabbit for long enough for the skin to seal.

One incision is made for the prescrotal, or ante-scrotal, approach on the ventral midline just cranial to the scrotal sacs. The testicles are pushed cranially into the incision and removed via either an open or closed technique. A subcuticular skin closure is used.

Castrated bucks should be kept isolated and quiet overnight. Castrated rabbits maintain mounting activity for a month or more, but other aggressive and sexual activities diminish rapidly. Castrated bucks should be kept away from intact does for at least 3–4 weeks after surgery.

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Abscess Removal

Rabbit abscesses are thick-walled and the pus is caseous. Surgical resection of the entire abscess is preferred to lancing and draining, which are often unsuccessful. Recurrence is common if the entire abscess capsule is not removed. Abscesses on the head should be radiographed to determine if there is bony involvement. Abscesses are commonly associated with dental disease, and total resection of these lesions is often not possible, carrying a fair-to-guarded prognosis, especially if there is an associated osteomyelitis. Different techniques can be employed to deal with odontogenic abscesses. The wound-packing technique consists of lancing and debriding the abscess and packing the cavity with antibiotic impregnated gauze strips (ampicillin or clindamycin 20 mg/kg). If a draining tract coming from the teeth is identified, the packing should be tightly applied at that location. The surgery is repeated every week until the infection is resolved, typically after 3–5 weeks. The marsupialization technique consists of removing the abscess content and capsule as much as possible and marsupializing the remaining capsule to the skin. The marsupialized area must then be flushed twice daily until it closes on its own. Retro-orbital abscesses can be approached through the area between the globe and the zygomatic arch.

Dental work up and dentistry should also be performed. As most of the bacteria involved in these abscesses are anaerobic, rabbits should be placed on systemic antibiotic with anaerobic spectrum such as oral azithromycin, oral metronidazole, or parenteral penicillin G. Antibiotic-impregnated beads may also be used in the treatment of odontogenic abscesses.

Enucleation

Indications for enucleation include lack of response to medical treatment for a number of intraocular disorders, corneal perforation, neoplasia, non-responsive glaucoma, and retrobulbar abscess. Skull radiographs or CT-scan may be necessary to detect bony lesions. Periodic buphthalmos can be associated with an intrathoracic mass, which can be confirmed with thoracic radiographs or CT-scan. Rabbits have a large intraorbital plexus, and significant bleeding is common during enucleation.

In rabbits, a transconjunctival approach is performed most commonly. The globe is dissected free from the conjunctiva through a circumferential bulbar conjunctival incision at the limbus. Sharp and blunt dissection is used to free the globe from the extraocular muscles, and a ligature or hemostatic clip is applied to the optic nerve and associated blood vessels prior to transection. After removal of the nictitating membrane and lacrimal gland, the eyelid margins are removed and sutured together. A large retrobulbar vascular plexus is present and its perforation may lead to significant hemorrhage. A ligasure® may be used to assist in enucleation surgery. If the plexus is perforated, packing the eye socket for 5 minutes and placing a piece of hemostatic foam are indicated.

The transpalpebral or en bloc approach involves suturing the eyelids together, incising the eyelid skin circumferentially, and dissecting as close to the bony orbit as possible, removing all structures. The optic nerve and vessels are ligated or a hemostatic clip applied. Skin edges are sutured together to close the orbit.

With either technique, antibiotic-impregnated polymethylmethacrylate beads may be implanted into the orbit to preserve normal contour and provide high levels of antibiotic locally.

Entropion

Entropion in rabbits is characterized by inward curling of the lid resulting in persistent conjunctivitis with discharge and blepharospasm. Corneal opacity, neovascularization, and ulceration may be additional signs. Surgical correction of entropion should be preceded and followed by topical and possibly systemic administration of antibiotics (e.g., trimethoprim/sulfa or enrofloxacin). Elliptical portions of affected lids are elevated and incised 2 mm from the entropic margin, as would be done in a dog or cat. Direct pressure on the incision line controls bleeding, and skin closure is with a simple interrupted pattern using 4–0 to 6–0 synthetic polymer sutures (e.g., nylon or polypropylene). Orbital lesions should regress within 14 days of surgery.

Conjunctival Hyperplasia

At least two conditions in rabbits involving the conjunctiva or nictitating membrane can be corrected by minor surgical procedures. A general, circumorbital ingrowth of a thickened, vascular, conjunctival fold over the cornea (aberrant conjunctival overgrowth or pseudopterygium) can be removed using fine forceps and scissors. Direct pressure applied for a few minutes controls hemorrhage. As conjunctiva frequently grows back, another approach may be necessary for long-term resolution. The conjunctival overgrowth is incised from the center to the limbus into six different segments. Each segment is then relocated within the fornix and fixed into place using mattress sutures through the skin.

Glandular or lymphoid hyperplasia of the nictitating membrane may produce a pea-sized lump in the region of the medial canthus. The mass is removed by incision into the lid surface lying against the eyeball; the cartilage is avoided. Fine absorbable sutures (5–0 or 6–0) are used to close the wound, and bleeding is generally minimal.

Rhinotomy

In cases of nasal empyema, abscessation, or foreign body (usually a piece of hay), surgical access to the nasal cavities may be necessary to debride, treat locally, and collect samples. Rabbits must be intubated during rhinotomies. Different techniques have been described, and the nasal cavity can either be approached dorsally (dorsal rhinotomy) through the nasal bone, ventrally (ventral rhinotomy) through the palatine fissure within the oral cavity, or laterally (lateral pararhinostomy) through the perforated surface of the maxillary bone. A rigid endoscope may be needed to improve visibility and

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assist with surgery depending on the technique. With a dorsal rhinotomy approach, the opening may be left open for further treatment (rhinostomy) in severe cases. The choice of the technique is based on imaging, in particular CT-scan, as the nasal cavity of rabbits is complex.

For a dorsal rhinotomy, the skin is incised using a scalpel blade and retracted. The periosteum is incised and retracted. The bone is then incised between the nasal bone and the incisive bone using a scalpel blade and the bony flap elevated. Alternatively, an orthopedic burr may be used for a less invasive access as guided from CT images. The nasal cavity is explored, debrided, and lavaged. Suction and rigid endoscopy may be used. The bone flap is either replaced or the rhinotomy is left patent and the periosteum and skin closed over. A catheter may be left in place to allow further antimicrobial treatment. For a lateral pararhinostomy, the skin is incised over the fenestrated area of the maxillary bone. There limited osteotomy is needed to access the nasal cavity. For a ventral rhinotomy, the oral mucosa is incised about 1 cm cranial to the first premolars and the underlying tissues are bluntly or sharply dissected until pus is encountered. An endoscope may greatly assist with ventral rhinotomies as the rabbit oral cavity is small.

Total or Partial Ear Canal Ablation and Bulla Osteotomy

This surgery is indicated in case of unresponsive and severe otitis externa and otitis media. With the total ear canal ablation and bulla osteotomy (TECABO), the ear may be flaccid following the surgery as the entire ear canal is removed. With subtotal TECABO or more partial ear canal ablation and bulla osteotomy (PECABO), the rabbit may conserve its normal ear carriage and the surgery is easier and faster. TECABO may also lead to partial necrosis of the pinna. Lateral subcutaneous abscess and lateral herniation of the pus-filled canal are also common with otitis externa. Lop-eared rabbits are most commonly diagnosed with ear diseases.

For the PECABO, the animal is positioned in lateral recumbency and a ventral skin incision is performed over the middle portion of the canal. The canal is dissected from the surrounding tissues. The canal is transected and the dissection is pursued to the bony acoustic meatus. The remainder of the canal is closed using a simple interrupted pattern. Then, the bulla is identified and entered with rongeurs. The bulla is debrided and gently curetted, and a culture sample is collected. Care should be taken not to damage the facial nerve in the area. Antibiotic PMMA beads or sustained-release antibiotic formulation (e.g., poloxamer 407 gel) are placed within the bulla. The surgical site is closed routinely.

For the TECABO, the entire external cartilaginous ear canal is removed following a T-shaped incision over the ear canal, further extended around the ear canal opening. The ear canal cartilage is then circumferentially dissected and transected at the level of the bony acoustic meatus. The bulla osteotomy is then performed as described above.

Thoracotomy

As the death rate following thoracotomy is high in rabbits, other treatments are preferred for thymoma. The treatment of choice is radiation therapy, which is noninvasive, well tolerated, and is associated with an average survival time of more than a year.

Orthopedic Procedures

Fractures of long bones are caused by inadvertent drops, improper restraint, dog or cat bites, limbs caught in cage wire, or territorial fighting between two does. Bones that are broken most often in rabbits are the tibia, femur, radius, and humerus (Figure 3.54). Overall, rabbits tend to have more complications following orthopedic surgery than other domestic animals do. Fractures in rabbits are usually closed and can be repaired as in cats; however, rabbit bones with thin cortices are fragile and light, and "thumping" can break down fixation devices. Internal fixation for midshaft fractures in otherwise healthy patients is achieved by open reduction and pinning with small IM pins or Kirchner wire(s) and external fixator devices. Skin sutures or clips are removed in 1–2 weeks, and pins in 4–6 weeks. Closed pinning techniques can produce good results in small animals. For external skeletal fixator, connecting bars can be made out of a Penrose drain filled with PMMA or the FESSA tubular external fixator can be used.

Limb amputations are well tolerated, but rabbits have fewer complications with front limb amputation than with the hind limbs, the main complication being pododermatitis.

Surgery in Rodents

Commonly performed surgeries in rodents include reproductive tract surgeries, abscess removal, lumpectomy and removal of mammary tumors, and urolith removal, as well as a large number of procedures performed for experimental purposes. As for rabbits, guinea pigs and chinchillas are prone to developing ileus and adhesions following abdominal surgery. With all rodents, careful attention to perioperative support, including provision of supplemental heat, replacement fluids, pain control, nutritional support, and gentle handling, is critical to facilitate recovery and healing in these delicate creatures.

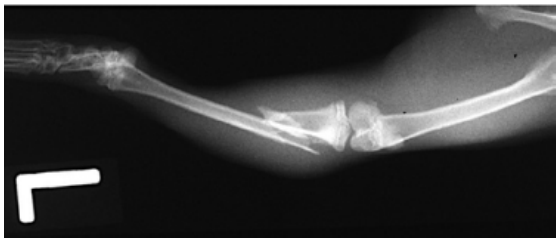


FIGURE 3.54. Lateral survey radiograph of a closed tibial and fibular fracture in a rabbit.

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Orchidectomy

Pet rodents are castrated to minimize fighting between males, to minimize odor, or as population control when males are housed with females. If improperly performed, bowel evisceration, strangulation, or herniation may result, with death of the pet as a possible sequela. A thorough appreciation of the reproductive tract anatomy of rodents is essential to prevent postoperative complications.

Rodents do not possess a discrete scrotum like the dog or cat; instead, the testicles are present within two separate scrotal swellings or sacs. The scrotal sacs are visible externally as a pair of swellings on either side of the penis. The tunica vaginalis lines each scrotal sac and is derived from an out-pouching of parietal peritoneum, which communicates directly with the peritoneal cavity through the inguinal canal. Each scrotal sac contains the large testicle, with its associated vascular supply, and a large fat body associated with the epididymis that usually extends into the inguinal canal. Unlike the dog or cat, this inguinal canal remains open throughout life, and in rodents and rabbits, the testicles may be withdrawn through this canal into the abdominal cavity. The diameter of the inguinal canal is so large that an incision into the tunica vaginalis is, in essence, an incision into the abdominal cavity. This is an extremely important consideration when performing an orchidectomy in these animals since failure to close the inguinal canal could result in serious postoperative complications, including evisceration and death.

Another anatomical consideration is the close proximity of the contaminated prepuce and anus to the surgical sites. Placing a cotton-tipped wooden applicator stick into the anal opening of larger rodents helps prevent passage of fecal pellets into the surgical field (Figure 3.55). In addition, the long prepuce of chinchillas can be secured cranially to the ventral abdomen with atraumatic tape to keep it out of the sterile field.

Closed, open, and abdominal castration techniques have been used in rodents. The closed technique is similar to that described for the rabbit. After surgical preparation and ensuring the testicles are in the scrotal sacs, the testicle is stabilized between thumb and forefinger and a 1 cm incision is made into each scrotal sac, taking care not to incise the tunica vaginalis. The testicle encased in the tunica vaginalis is dissected free, so that the tunica-encased cord is exposed. After crushing with a hemostat, a transfixing ligature is placed through the cord, and the testicle and tunica vaginalis are transected distal to the ligature. The skin incision is closed with skin sutures or sterile tissue glue, taking care not to get any glue on the skin surface, which may incite the animal to chew at the area. This technique eliminates any opening into the abdominal cavity, and the transfixing ligature provides added security against slippage of the ligature. However, dissection of the tightly adherent skin from the tunica vaginalis can be time consuming.

With an open technique, which involves incising through the skin and tunica vaginalis, care must be taken to prevent postoperative herniation of viscera into the scrotal sac. One method is to leave behind the epididymal fat pad to block the inguinal opening, prior to suturing the skin. However, herniation of the bowel or bladder may still occur following this technique. A superior method involves ligating the spermatic vessels but leaving the gubernaculum attached to the tunica vaginalis. By applying tension to the testicle, the attached tunic can be stretched taut and easily dissected free from the surrounding skin, after which a transfixing ligature is placed as close to the inguinal opening as possible, taking care not to incorporate any vessels or viscera. Skin is closed as for the closed technique (Figure 3.55). An alternate technique in rats involves making a single 1 cm midline incision at the distal scrotal tip, pushing the testicles caudally, and cutting each tunic. Each testicle and epididymis is exteriorized, and the cord is ligated. The skin is closed with 9 mm clips, taking care not to clip the anus shut.

In the abdominal technique, a ventral midline incision is made over the caudal abdomen, the testicles are pushed from the inguinal canal into the surgical site, spermatic cord is ligated, and testicles removed, followed by routine closure of the abdominal wall, using a subcuticular pattern. The abdominal technique is the preferred method in guinea pigs as it has been associated with fewer post-operative complications.

Ovariohysterectomy

Indications for ovariohysterectomy include prevention of pregnancy and mammary gland tumors and treatment of dystocia, pyometra, and cystic ovaries. The reproductive anatomy of female rodents resembles that of the dog and cat, except in rats, which have two cervices. After surgical preparation, a ventral midline incision is made, taking care not to lacerate underlying viscera. The uterine horns are located and traced cranially to the ovaries. The ovarian pedicles are ligated, as are any large vessels in the broad ligament. The uterus is ligated caudal to the cervix. The abdominal wall is closed using appropriately sized synthetic suture material in a simple continuous or simple interrupted pattern, followed by a subcuticular closure of the skin or careful use of tissue glue. In guinea pigs, because of the presence of the large GI tract and the dorsal locations of the ovaries, the ovaries cannot be exteriorized fully and the ovarian suspensory ligament may be broken blindly or hemoclips may be used.

Ovariectomy

Ovariectomy are commonly conducted in rodents for research purposes and also for neutering companion animals. The rodent is placed in sternal recumbency, and the skin is clipped over the lumbar spine and flanks. A transverse flank incision is made on each side 0.5–1 cm caudal to the last rib and ventral to the epaxial muscles. Alternatively a single 1–1.5 cm dorsal midline incision is made and shifted to either side of the flank over this area. Subcutaneous

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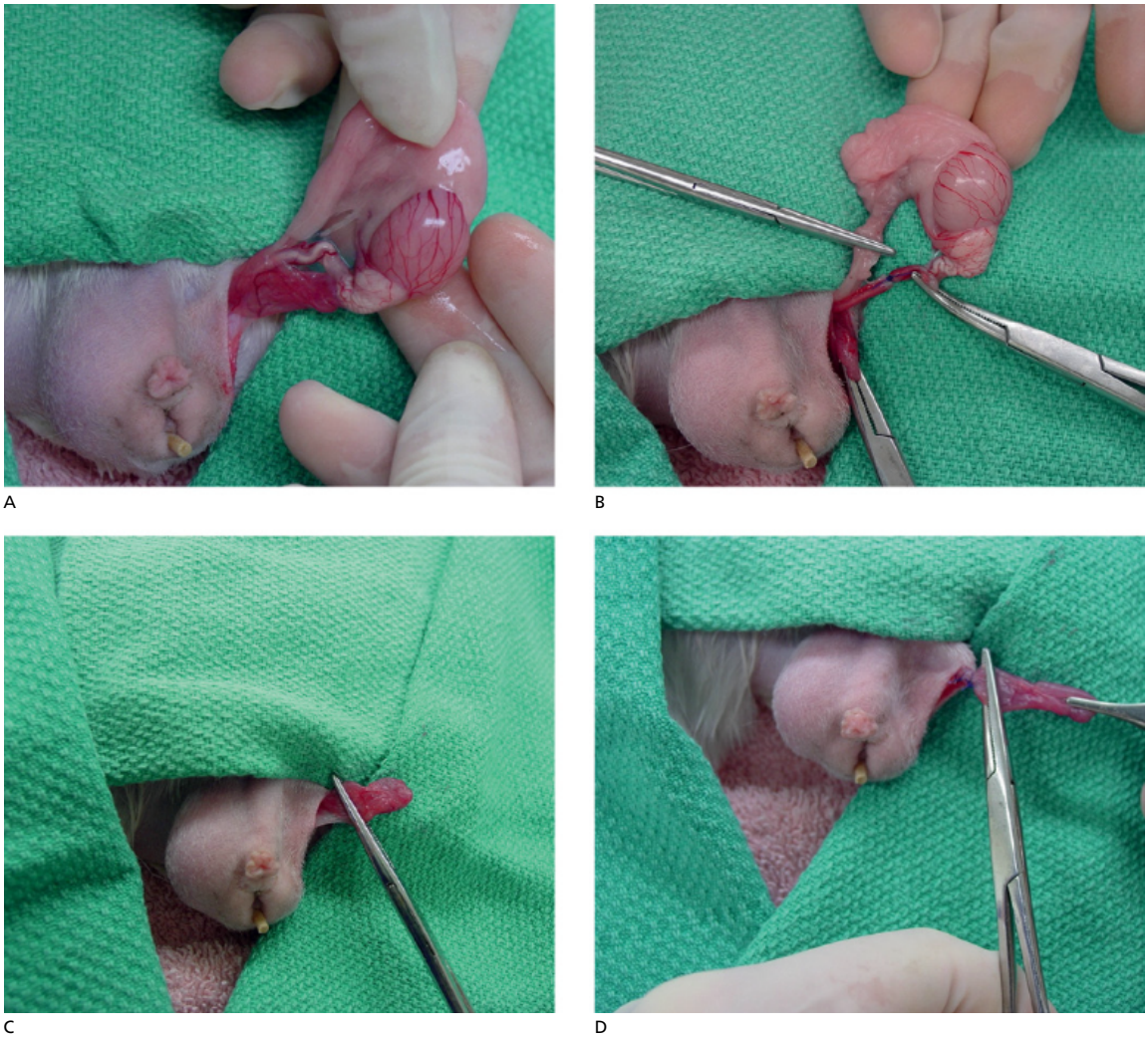


FIGURE 3.55. Open technique for guinea pig castration. A: After incising the skin and tunic, the testicle and fat pad are exteriorized. B: The tunic is teased away from the testicle by tearing the gubernaculum (bottom clamp), and the spermatic cord and any vessels in the fat pad are clamped and ligated. C: The ligated stumps are allowed to retract back into the abdomen and the tunic is clamped as proximally as possible, taking care not to entrap the stumps. D: A transfixing ligature is placed at the proximal end of tunic, effectively closing the inguinal canal. The excess tunic is then trimmed away, and the skin closed with sutures or tissue glue. A cotton applicator with the stick cut short has been placed in the anus to prevent fecal pellets from contaminating the site. Courtesy of Dennilyn Parker.

tissues and abdominal wall muscles are separated, and the peritoneum punctured approximately 5 mm off midline to reveal and permit extraction, ligation, and transection of the fat-imbedded ovary through the flank incision. The oviduct may also be removed at the same time; bleeding rarely occurs following this procedure. Metal clips or 4–0 or 5–0 sutures can be used to close the body wall and should be removed within 7 days of surgery. Tight skin sutures should be avoided to reduce irritation and subsequent chewing at the incision.

Abscess Removal

Rodent abscesses are often circumscribed by dense fibrous capsules and generally contain thick, purulent material, often due to a mixture of aerobic and anaerobic bacteria. If not amenable to surgical removal in toto, abscesses should be lanced, flushed, and left open to drain, or implanted with antibiotic-impregnated polymethylmethacrylate beads or antimicrobial-impregnated gauze and closed. Culture and sensitivity of the abscess capsule for both aerobic and anaerobic organisms

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should be done to guide systemic antibiotic choice, keeping in mind that many antibiotics are toxic in some rodents. Odontogenic abscesses are treated similarly to rabbits.

Submandibular abscesses in guinea pigs may be due to infection of lymph nodes with *Streptococcus equi subsp. zooepidemicus,* and septicemia may result if these are not opened and drained. Surgical resection may be challenging due to close association with the vagal nerve, jugular vein, and carotid arteries. Treatment may be restricted to lancing, cleaning, and systemic antibiotics.

Lumpectomy

Skin and subcutaneous lumps are common in rodents. Benign mammary tumors in rats may be very large and are generally easily removed, although larger tumors often become necrotic and highly vascularized. Trichofolliculomas are common in guinea pigs. Prior to surgery, the surgeon should ensure that there is adequate skin to close the incision. For mammary gland tumor surgery, the rat is anesthetized, and the encapsulated tumor is removed through a cutaneous incision. Ligation of connecting blood vessels is necessary. Mammary tumors in mice and many other skin tumors, such as fibrosarcomas, are locally invasive and may be difficult to completely remove. Sebaceous adenomas in guinea pigs can become quite large and are filled with caseous sebum, which should not be confused with pus. Guinea pigs have a moderate amount of loose skin over the dorsum, which facilitates excision. Skin sutures may be placed in areas inaccessible to the rodent's teeth.

Cystotomy

The primary indication for cystotomy in rodents is to remove urinary calculi, typically made of calcium carbonate. Calculi may be present in the urethra, urinary bladder, ureters, or renal pelvices (Figure 3.56). Signs of calculi and cystitis include hematuria, urine dribbling, anorexia, and evidence of pain and distress. A radiograph may confirm the presence of urinary calculi. A kidney may be enlarged because of hydronephrosis or renal calculi.

The surgical procedure is similar to that in rabbits, although preplacement of a urethral catheter may not always be possible. Urine culture and sensitivity and culture of a piece of the urinary bladder wall should be performed to determine if antibiotic therapy is indicated. Urinary calculi often recur.

Fracture Repair

Fractures of long bones are caused by being dropped, being bitten by dogs or cats, or catching limbs in cage wire. Bones most often broken are the tibia, femur, radius, and humerus (Figures 3.57 and 3.58). Tibial fractures are particularly common in chinchillas. As in rabbits, complications are common in chinchillas and guinea pigs. Adjuncts to fracture repair may be fluid therapy for shock and quiet housing to reduce stress.

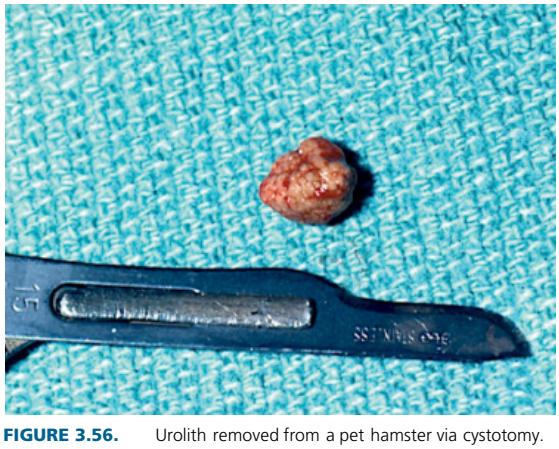


FIGURE 3.56. Urolith removed from a pet hamster via cystotomy.



FIGURE 3.57. Hamster with fractured femur.



FIGURE 3.58. Male gerbil with tibial fracture repaired by external fixation. The ventral marking gland is visible on the abdomen and is developing a neoplastic growth at its caudal end.

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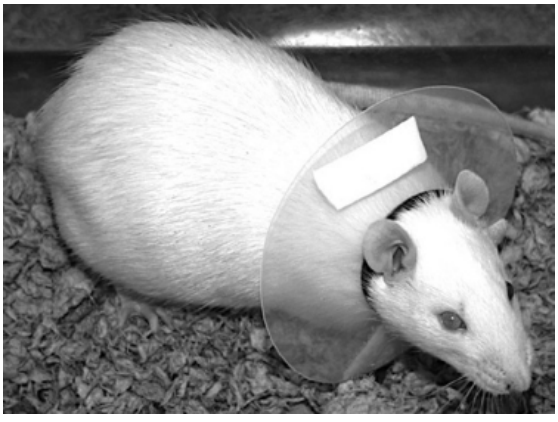


FIGURE 3.59. Elizabethan collar fitted for a rat.

Nonscreen radiographic film techniques may be needed to reveal fractures in small bones, and anesthesia must be adequate to relax muscles and allow reduction of the fragments. An anatomic characteristic other than small size that increases the challenge of fracture repair in small rodents is the enclosure of femurs and humeri in the trunk mass or the abdominal skin. Internal fixation for midshaft fractures in otherwise healthy patients is achieved by open reduction and pinning with small pins, Kirschner wires, spinal needles, or hypodermic needles. Skin sutures or clips are removed in 1–2 weeks, and pins in 4–6 weeks. Closed pinning techniques produce good results in small animals. An Elizabethan collar may be useful to prevent the animal from chewing at the affected area (Figure 3.59).

The FESSA tubular external skeletal fixator is also useful in small patients. External fixation devices, including taping the affected limb to the body wall and splinting with rolled film or small sticks, are often unsuccessful because of self-mutilation. Traction casts, consisting of a taped foot drawn through a plastic syringe cover, may be successful, although the usual outcome is chewing and self-mutilation. The foot is bound to a piece of adhesive tape, the broken limb pulled almost through the tube, and the tape wrapped to the distal end of the tube. Padding in or around the tube openings may be necessary. Casts and splints are more practical for forelegs rather than for rear legs. An additional treatment option in smaller rodents that is often preferred is to provide nothing more than cage rest and allow the limb to heal with the possible complication of malunion.

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DENTAL PROCEDURES IN RABBITS AND RODENTS

All teeth of rabbits, guinea pigs, and chinchillas are elodont (continually growing), while in hamsters, gerbils, rats, and mice only the incisors grow continually. Rabbits have two pairs of maxillary incisors (one behind the other) and one pair of mandibular incisors, while rodents have only one pair of maxillary incisors and one of mandibular incisors. In addition in rabbits and hystricomorph rodents, the teeth don't have roots (aradicular), have high clinical crowns (hypsodont), have enamel ridges on their occlusal plane (lophodont), and have several subunits (polylophodont). Rabbits are anisognathic with the maxillary arch wider than the mandibular arch, have bilophodont teeth, a dental plane of about 10–20°, and have straight dental rows. Guinea pigs and chinchillas are also anisognathic but differently than the rabbit since the maxillary arch is narrower than the mandibular arch. The dental plane is also different and is 0° in chinchilla and about 40–60° in guinea pigs. Chinchillas have trilophodont cheek teeth while they are bilophodont in guinea pigs. In guinea pigs, the dental rows converged rostrally and the cheek teeth have marked intraalveolar curvatures. While normal incisor occlusion in the rabbit consists of the bottom incisors resting on the peg teeth, in rodents, the incisors don't touch in normal resting occlusion. In myomorph rodents, the cheek teeth are similar to other domestic mammals and humans and are radicular, bunodont, an anelodont.

Dental disease is a global term encompassing a wide range of disorders. Incisor malocclusion can be congenital or acquired. When it is congenital, it is often caused by maxillary

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brachygnathism. When it is acquired, it is often caused by cheek teeth elongation and malocclusion. Cheek teeth disease is typically characterized by a combination of disorders including reserve crown elongation, clinical crown elongation, shifting of the dental plane, buccal or lingual spurs (Figures 3.60 and 3.61), increased curvature of the crowns, dentin hypoplasia, soft-tissue ulcers in the oral cavity, cavities (in particular in chinchillas), abscessation, osteomyelitis, and periodontal disease. In addition, dental disease may cause or promote a variety of disorders in other organ systems including dacryocystitis, dermatitis from lack of grooming, retroorbital disease, odontogenic rhinitis, odontogenic abscesses, and gastrointestinal stasis. Vitamin deficiencies, in particular vitamin D in indoor rabbits and vitamin C in guinea pigs, may also promote dental disease. Other causes include genetic selection and inadequate diet with too much high-energy low-abrasive food such as pellets and a lack of abrasive food and non-digestible fibers such as grass and hay.

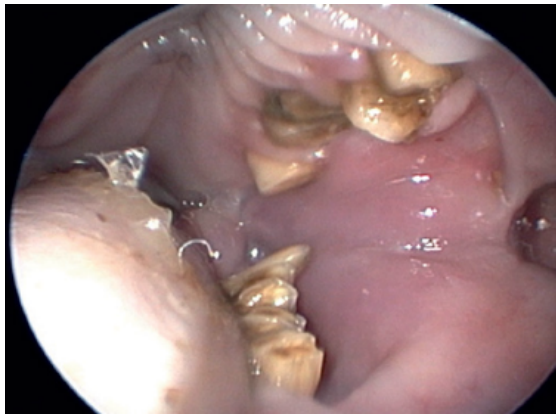


FIGURE 3.60. Advanced dental disease in a pet rabbit, view of the left arcades. The dental plane is completely disrupted, dental spurs are present, gingival hyperplasia is present, and mild overgrowth of clinical crowns is also evident.



FIGURE 3.61. Advanced dental disease in a guinea pig. The clinical crowns are elongated, the dental arcades are asymmetric, and mild "bridging" of the mandibular premolars is present.

Dental procedures are challenging due to the small size and gape of the oral cavity. Access to the incisors poses little problem; however, recognition of their normal length and appearance is critical to avoid unnecessary trimming, which could harm the animal and interfere with food prehension. Access to premolars and molars is more difficult, and care must be taken to guard against trauma to the cheeks, gums, and tongue while performing dental work. Dental specula and cheek dilators are commercially available for pet rabbits and rodents and will assist with viewing the cheek teeth (Figure 3.62). Dental tables are also available for rabbits and rodents and are more convenient to use. The use of a rigid endoscope (video otoscope or long rigid endoscope) is strongly recommended for a thorough dental examination and video documentation (Figure 3.62). A good dental examination without an endoscope or other means of magnification may simply not be possible in smaller rodents such as chinchillas.

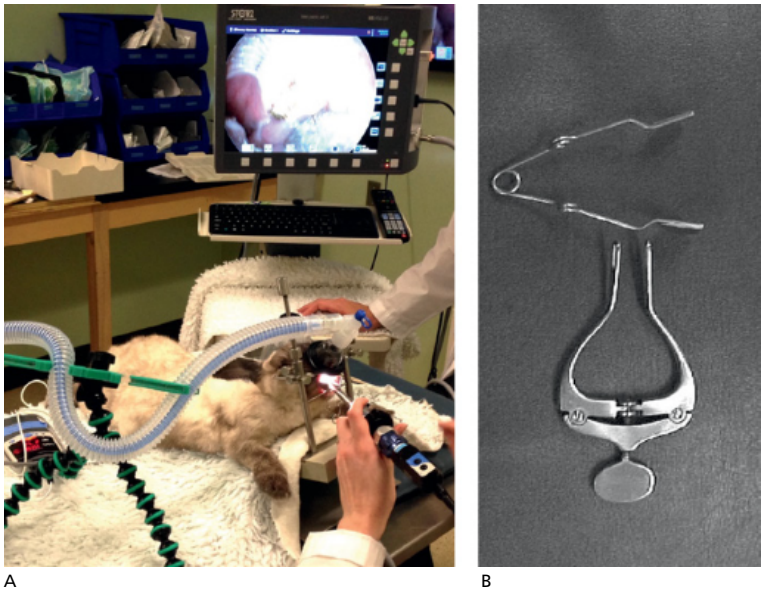
Dental trimming and occlusal adjustment must be performed using a low-speed rotating dental instrument with a straight piece. Small diamond coated burrs of different shapes can be used for molar trimming while a cutting disc is typically employed for incisor trim. Soft tissues should be protected using tongue depressors, other metallic instruments, or a soft tissue protector sleeve around the rotating burr. Debates exist as to whether maximal shortening of the clinical crowns of the molars is needed or if one should just trim all the spurs and shorten overgrown molars to re-equilibrate the dental plane (Figure 3.63). If cavities are identified (e.g., chinchillas), the molar should be shortened maximally so as to remove most or all of the necrotic dental tissue. Manual rasps are not recommended as pain may be higher and micro-fractures of the teeth and apical trauma may occur. Trimming may be necessary every 1–12 months depending on the severity and rate of growth and dental disease requires life-long treatments. See Table 3.17 for a listing of dental formulas.

Clipping or sawing the teeth in conscious animals predisposes to development of rough edges, vertical fractures with pulp exposure, and tooth root abscesses, and may be painful and stressful for the rabbit and for the client. It is strongly discouraged and not considered humane.

The elodont teeth of rabbits, particularly the incisors, may be removed as a cure for congenital or severe acquired malocclusion and the associated overgrowth, particularly when tooth trimming may be required at very frequent intervals. Opposing teeth must also be removed. To extract an incisor tooth, the patient is anesthetized, radiographed to determine condition and location of the apex, and given an antibiotic (e.g., enrofloxacin, azithromycin, metronidazole) if abscessation is suspected.

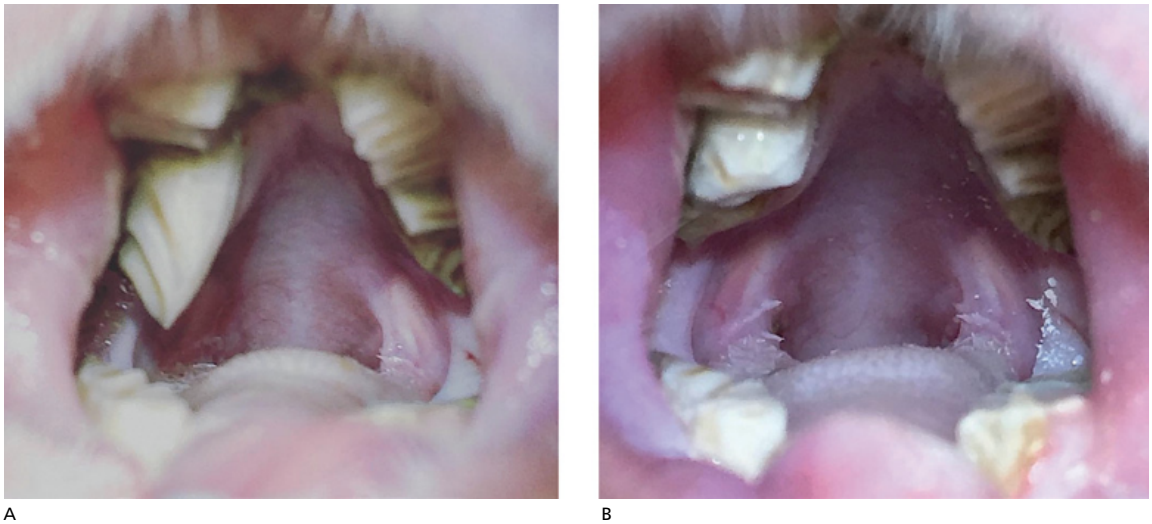
Periodontal ligaments, especially those on medial surfaces of the incisors, are broken down using a dedicated rabbit incisor luxator, small elevator, root tip pick, or bent 18-gauge needle. The loosened teeth are first pushed to free them from the

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A B

FIGURE 3.62. A: Stomatoscopy and dental examination in a companion rabbit. B: Incisor speculum and cheek dilator for rabbits.



A B

FIGURE 3.63. Chinchilla teeth before (a) and after (b) molar trim. Courtesy of Calgary Avian & Exotic Pet Clinic.

ligaments, then pulled using gentle pressure with an extractor or forceps and pulling along the curvature of the teeth. The remaining odontogenic tissue may be destroyed with a curette and the alveolae are flushed with 0.05% chlorhexidine. Care should be taken not to insert the luxator too deeply into the maxilla so as not to penetrate the nasal cavities. Lower incisors are removed first. The smaller, upper caudal incisors have straight reserve crowns that can be removed easily but may break. If crowns are broken (the root is soft and hollow), the remaining tooth root will generate and erupt as a tooth in 6–8 weeks.

Cheek tooth removal is more difficult. Intraoral extraction may be performed using a dedicated rabbit cheek teeth luxator and a forceps. Intraoral extraction is easier in loose and diseased molars. An extraoral extraction may also be performed following an osteotomy of the ventral mandible. Open sockets are flushed with an antiseptic, or apical areas may be cultured if an abscess is suspected, and the rabbit given antibiotics for several days.

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Table 3.17. Dental formulas of rabbits and rodents.

Species		Incisors	Canines	Premolars	Molars
Rabbit	2×	$\frac{2}{1}$	$\frac{0}{0}$	$\frac{3}{2}$	$\frac{3}{3}$
Guinea pig	2×	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{1}{1}$	$\frac{3}{3}$
Chinchilla	2×	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{1}{1}$	$\frac{3}{3}$
Hamster	2×	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{3}{3}$
Gerbil	2×	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{3}{3}$
Rat	2×	$\frac{1}{1}$	$\frac{0}{0}$	$\frac{0}{0}$	$\frac{3}{3}$

QUALITY ASSURANCE PROGRAMS FOR COLONY HEALTH SURVEILLANCE

Routine health monitoring (HM) is an essential part of managing populations of research animal. The goal of these programs is to maintain these animals free of naturally occurring pathogens that may cause clinical or subclinical infections, compromise animal welfare, or alter experimental results. Historically, serology was the primary method for monitoring the disease status of SPF rodent and rabbit colonies. Indirect enzyme-linked immunosorbent assay (ELISA) served as the primary screening method for serosurveillance. The ELISA is performed as a singleplex, in which one microbial antigen–antibody reaction is measured per well. In contrast, the multiplexed fluorometric immunoassay (MFIA) can identify the presence of multiple agents. The MFIA suspension microarray uses color-coded polystyrene 5.6 µm beads to which antigens (or controls) are covalently linked. Because the microspheres come in 100 distinct color sets, as many as 100 different assays can be performed simultaneously in a single microplate well. This decreases the amount of serum, reagents, and disposables required for routine testing while increasing the amount of information obtained from a single test well.

Viral infections in conventionally housed rodents are moderately common and may influence health and experimental results, especially mouse hepatitis virus and parvovirus infections, which are among the most common diseases of laboratory mice in North America and the EU. The detection of rodents carrying antiviral antibodies, and possibly the virus itself, is an important consideration in disease prevention in rodent colonies whether bred for research or for the pet trade. Viral agents are typically monitored by a combination of pathogen detection systems (polymerase chain reaction [PCR], histopathology, viral culture) and serodiagnosis.

Adventitial bacterial diseases also may cause significant complications in research colonies. Many of the more common pathogenic organisms, such as *Salmonella* spp. and *Bordetella* spp. in all species and *P. multocida* in rabbits, have been eliminated by selective breeding or embryo rederivation. The presence of these agents is typically monitored by culture and serology. Many of these agents are not transmitted well by soiled bedding sentinel (SBS) systems either because of low prevalence or because they require direct contact between animals for detection.

For rodent colony health surveillance, SBS HM programs have traditionally been used, which rely on fecal–oral transmission of agents between the colony animals and the sentinel animals. At each cage change, a fixed amount of soiled bedding is transferred from colony cages to sentinel cages. There are many different approaches for SBS HM programs, and veterinary consultation is needed to optimize the list of agents to test for, the type of diagnostics used, the frequency of testing, and the numbers, age, and strains of animals used for SBS to optimize detection of agents being monitored. At the end of a fixed period of exposure, for example, quarterly, sentinel animals are bled and serum with or without other samples, such as fecal pellets, swabs, and tissues are sent for diagnostic testing. Programs may additionally include direct sentinel or colony animal testing through physical examination, serology, PCR, bacterial culture, necropsy, and histopathology. Globally, tens of thousands of mice and rats have been used each year for SBS, and this has spurred the development of alternative approaches to replace live animal systems for quality assurance HM programs.

Recently, environmental PCR testing has emerged as an adjunct or replacement method for SBS testing. This approach is accomplished by swabbing then PCR testing exhaust air dust from the IVC rack plenum, swabbing the cage interior or soiled

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bedding from colony animals, swabbing animal hair directly (for fur mites), or collecting swabs from the room and equipment. These approaches, while not necessarily suitable for all housing systems, have been found to be highly sensitive for many pathogens, including fur mites, which transferred poorly if at all to sentinels in SBS systems. Use of exhaust air duct and related swabbing/PCR techniques has resulted in a significant decrease in the numbers of animals used for SBS testing. These systems do not completely replace the need for other types of HM programs. For example, *Helicobacter* spp. are commonly detected in research colonies and can be diagnosed by histopathology, culture, PCR, or serology. Similarly, parasitic diseases such as mites in mice, hamsters, and rabbits, or pinworms in all species may be occasionally diagnosed in a laboratory setting, typically by direct observation of the adult or ova. PCR assays are highly sensitive but may occasionally lead to false positive results, and it is always best to discuss unexpected diagnostic results with the lab to assist with decision-making in colony management.

Use of barrier housing, quarantine, health screening for incoming animals, and routine health surveillance of sentinel or experimental animals are strategies used to maintain and monitor colony pathogen status and are similar to those implemented for large groups of agricultural animals (i.e., a "herd health approach"). The scope and characteristics of a health monitoring program are unique for each facility, and include consideration of size of the program, types of research, presence of immunodeficient animals, source of animals, types of housing, and many other factors. A detailed discussion of program development is outside the scope of this review. Several publications review the rationale and recommendations for development of a program for monitoring and surveillance of diseases in rabbit and rodent colonies.

Sentinel Testing Procedures

Commercial laboratories that provide the majority of rodent serology testing do so primarily for the research community. Several of these labs also offer services to clinical practitioners, which might be useful for diseases such as *Encephalitozoon* spp. infection of rabbits or lymphocytic choriomeningitis virus (LCMV) infections of hamsters or mice. Laboratories have traditionally used ELISA as a screening tool to measure antibodies to organisms associated with clinical or subclinical disease in rodents. Positive results are typically confirmed by most laboratories using a more specific technique, such as indirect fluorescent antibody or Western blot analysis. Multiplex fluorescent immunoassay (MFI) is a type of liquid-phase bead-based ELISA assay that makes use of flow cytometric technology. This technique permits screening of multiple antibodies with one serum sample. Because only 0.2 µL of undiluted serum can be used to test reactivity against a large number of pathogens, this technique is highly suitable for screening rodent samples and has been developed by major rodent serologic diagnostic laboratories.

PCR testing is also available for many diseases of research and companion rabbits rodents. Many of the PCR assays can be run using fecal samples. Clinicians should remember that the PCR test will only indicate infection when the agent is being shed, which may be a short period of time for acute infections that result in complete recovery. This is typically the period before serum antibody response has occurred, and it is feasible to use PCR to screen for active pathogen replication and serology to evaluate recovered or persistent infection. Table 3.18 summarizes the more common serologic tests suggested for screening sera from various species.

Table 3.18. Summary of common rabbit and rodent diagnostic tests.

Virus	Species Tested	Primary Test	Secondary Test	Prevalence
PVM	M, R, H, Gp, (Rb)	E/MFIA	IFA, Path, PCR	Rare. Minimal lung lesions in immunocompetent mice. Progressive interstitial pneumonia with wasting in immunodeficient mice.
Reo-3	M, R, H, Gp	E/MFIA	IFA, PCR, HAI	Low to moderate
TMEV	M, R	E/MFIA	IFA	Moderate to common. Also called TO or GDVII
Rat virus (KRV)	R	E/MFIA	IFA, HAI, Path, PCR	Common but rarely produces disease—abortions and resorptions; In adults: hemorrhagic encephalopathy, congestion of lymph nodes, loss of body fat, scrotal hemorrhage
H-1 (Toolan's H-1 virus)	R	E	IFA	Rare

(*continued*)

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Table 3.18. ***(continued)***

Virus	Species Tested	Primary Test	Secondary Test	Prevalence
K virus	M	E/MFIA	IFA, PCR	Very rare—need for testing in question
MVM	M	E/MFIA	IFA, HAI	Common—orphan parvo viruses cross-react in diagnostic tests
Polyoma	M, (H)	E/MFIA	IFA, PCR	Very rare
Sendai	M, R, H, Gp	E/MFIA	IFA, Path, PCR	Very common in pet and wild rats and mice—lung lesions; rare in laboratory rodents
MHV	M	E/MFIA	IFA, Path, PCR	Common—many strains of virus, Syncytia in many tissues, including intestine
SDAV/RCV	R	E/MFIA	IFA, Path	Common in pet rats—many strains of virus, salivary and Harderian gland lesions; rare in laboratory rats
SV-5	H, Gp	E	IFA, HAI	Rare in laboratory rodents, unknown prevalence in wild rodents—significance unknown
EDIM	M	E/MFIA	IFA, Path	Low to moderate
Adenoviruses	M, H, (R)	E/MFIA	IFA, Path	Common in hamsters and conventional mice
Ectromelia	M	E/MFIA	Path, IFA, PCR	Uncommon—may cause high mortality in certain strains
LCMV	M, H, Gp, R	E/MFIA	IFA, PCR	Uncommon—zoonotic disease
LDHV	M	LDH plasma enzyme assay	PCR	Uncommon in laboratory mice, common in wild mice. Colorimetric assay. No clinical signs
Mouse thymic virus	M	E	IFA, Path, CF, PCR	Rare in laboratory mice, common in wild mice. Thymic necrosis in neonates
Cytomegaloviruses	Gp, R, M	E/MFIA, IFA	Path, PCR	Common in guinea pigs—causes lesions in salivary glands
Mycoplasma pulmonis	R, M	E/MFIA, IFA	Culture, Path, PCR	Rare in laboratory animal colonies. Common in pet and wild rats and mice—readily cultured
Filobacterium rodentium (CAR Bacillus)	R, Rb, M, Gp, H	E/MFIA	Path, IFA, PCR	Common in pet populations—silver stain of respiratory epithelium
Tyzzer's Disease (*Clostridium piliforme*)	M, R, H, Gp Gb, Rb	E/MFIA	Path, IFA, PCR	Common
Encephalitozoon cuniculi	Rb, Gp, H, M, R	E/MFIA	Path, IFA, PCR	Common

M, mouse; R, rat; H, hamster; Gp, guinea pig; Rb, rabbit; Gb, gerbil; CF, complement fixation; IFA, immunofluorescence; HAI, hemagglutination inhibition; ELISA, enzyme-linked immunosorbent assay; MFIA, multiplexed fluorometric immunoassay; Path, histopathology helpful, in parentheses—indicates the test is not commonly performed.

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OTHER SPECIAL TECHNIQUES

Administration of Substances

Oral

The method of administering a substance by mouth depends on whether one animal or many animals are being treated, and whether the animal is a companion or part of an experimental study. Rabbits and rodents may voluntarily accept oral medications if they are available in a palatable, liquid form, which may require mixing with flavored syrup, or the assistance of a compounding pharmacy (Figure 3.64).

Force-feeding by syringe requires firm restraint, gentle insertion of a 1–3 mL syringe partway into the oral cavity via the diastema, slow injection, and careful cleaning of the face area afterward for patient comfort. Use of a small syringe allows for placement further within the oral cavity and is generally more successful than using a 5 mL or larger syringe, even if refilling must be done more often. Alternatively, a catheter-tip 30 cc or 60 cc syringe may be used.

In experimental studies, in which accurate administration of a dose is usually critical, direct delivery of the substance into an animal's esophagus or stomach may be required. The most stressful part of the procedure for animals is the restraint, and animals can be gradually habituated to restraint prior to study to reduce and eliminate associated distress. Taking this time to habituate animals, for example, over a 2-week period prior to the study starting, can significantly reduce animal injury due to struggling and misdosing.

In rabbits a premeasured, lubricated, 8–10 Fr infant feeding tube or soft catheter can be passed directly into the oral cavity or through a speculum, such as an open-ended 3 mL syringe barrel, to prevent chewing. Placement of the tube can be verified by aspiration (if air comes back freely, the tube is likely in the lungs), injecting air into the tube while listening for



FIGURE 3.64. Hamster voluntarily consuming medication. Courtesy of Calgary Avian & Exotic Pet Clinic.

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gurgling over the stomach, and palpating the cervical area for the presence of both the trachea and the feeding tube. Rabbits rarely struggle or vocalize if intubated incorrectly such that confirmation before administering the dose is critical.

Placement of a nasogastric or esophagostomy tube can also be done if repeated administrations are necessary, or with anorexic pet rabbits that require nutritional supplementation and that do not tolerate manual force-feeding. Nasogastric tube placement requires topical anesthesia in the nostril and is not technically difficult to perform. However, the small tube diameter allows only liquids to pass, the tube may interfere with nasal breathing, and rabbits may dislodge the tube from their nose during grooming (Figure 3.65). Elizabethan collars can be placed but add to animal discomfort. Specific diets are available for nasogastric feeding in rabbits such as Oxbow Critical Care Fine Grind®. Esophagostomy tube placement requires general anesthesia; however, postoperative animal comfort is greater, breathing is not compromised, and tubes are rarely pulled out. The larger diameter allows food with more substance to be given. Placement is performed similar to that for a cat. Direct intranasal administration of substances is commonly required in research settings and can be readily accomplished in sedated or anesthetized animals (Figure 3.66).

Plastic (preferred) or curved, ball-tipped metal feeding needles are commercially available for oral dosing of rabbits and rodents. Rodents are restrained firmly in an upright position with the head tipped upward with restraint or using the fingers encircling the shoulders to tip the head. Gravity and the swallowing reflex will facilitate passage into the esophagus—force should never be used as esophageal rupture may occur (Figure 3.67). If the needle does not pass easily, it should be removed and repositioned. Respiratory distress may occur if animals are restrained too tightly or if the needle inadvertently enters the trachea or ruptures the esophagus.



FIGURE 3.65. Nasogastric tube in a rabbit. For chronic administration of fluid or food, the tube has been secured in place and affixed to the skin of the head.

Use of a disposable plastic water bag, such as a Sipper Sack®, can be used to administer a specific concentration of a substance over a set period of time, for example, 24 hours pretreatment with a specific antibiotic prior to administration of a pathogen, in infectious disease research models. However, administration of substances via the drinking water is not suitable for all substances, and provides an inexact dose to each animal in the enclosure, which must be taken into consideration if this method is considered as a treatment.

Administration of pills or capsules to rodents and rabbits can be challenging. Most guinea pigs will willingly take flavored vitamin C tablets, or the tablet can be pushed back behind the fleshy cheek invaginations, which stimulates a

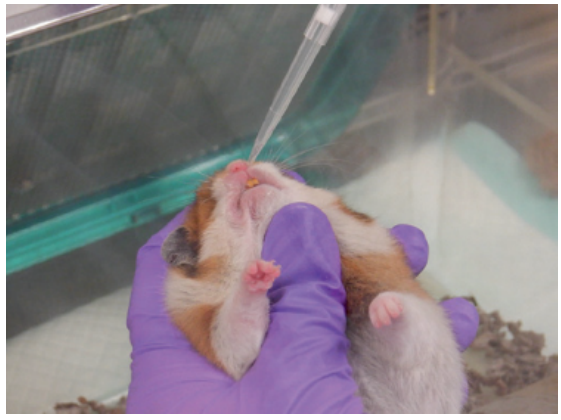
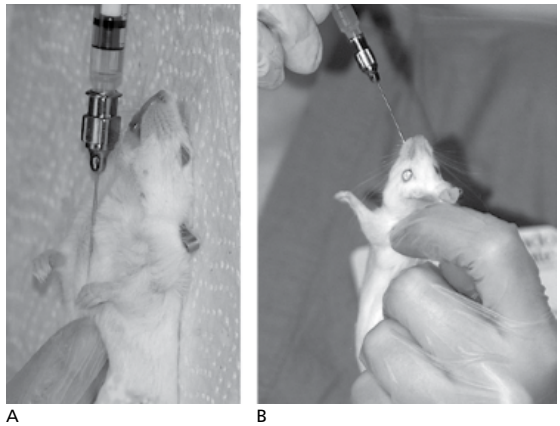


FIGURE 3.66. Intranasal administration of substances can be accomplished readily in a sedated or anesthetized animal as seen for this hamster.



A B

FIGURE 3.67. The length of gavage needle to be inserted should always be measured externally on the animal to minimize the likelihood of injury (A). For intragastric gavage, the end of the needle should extend to the xiphoid. The animal must be restrained firmly to minimize struggling and prevent injury (B).

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chewing response. Small tablets may be hidden in pieces of food, such as raisins, or crushed and mixed with Ensure or other palatable food or liquid. Cat pill dispensers may be useful in larger rodents and rabbits. Care must be taken not to traumatize the palate or oral tissues, which may result in anorexia.

Parenteral

Administration of substances via the subcutaneous, intradermal, intramuscular, intraperitoneal, and intravenous routes is straightforward. Rodents can be loosely covered with a small towel or cloth if injections are conducted by one person. Intramuscular injections occasionally result in muscle necrosis and self-mutilation in smaller rodents, especially mice, so must be given with care, and the site monitored closely afterward. Because of the small muscle mass, many substances given IM in other species, e.g., ketamine combinations, are better given SC in rodents, although this will result in slower absorption and slightly longer times to occurrence of peak blood drug levels. Other routes of parenteral administration, such as nebulization or intraosseous catheterization, require specialized equipment, and may be more technically challenging to perform. The intraosseous route may be used for fluid or blood administration if intravenous cannulation is not possible.

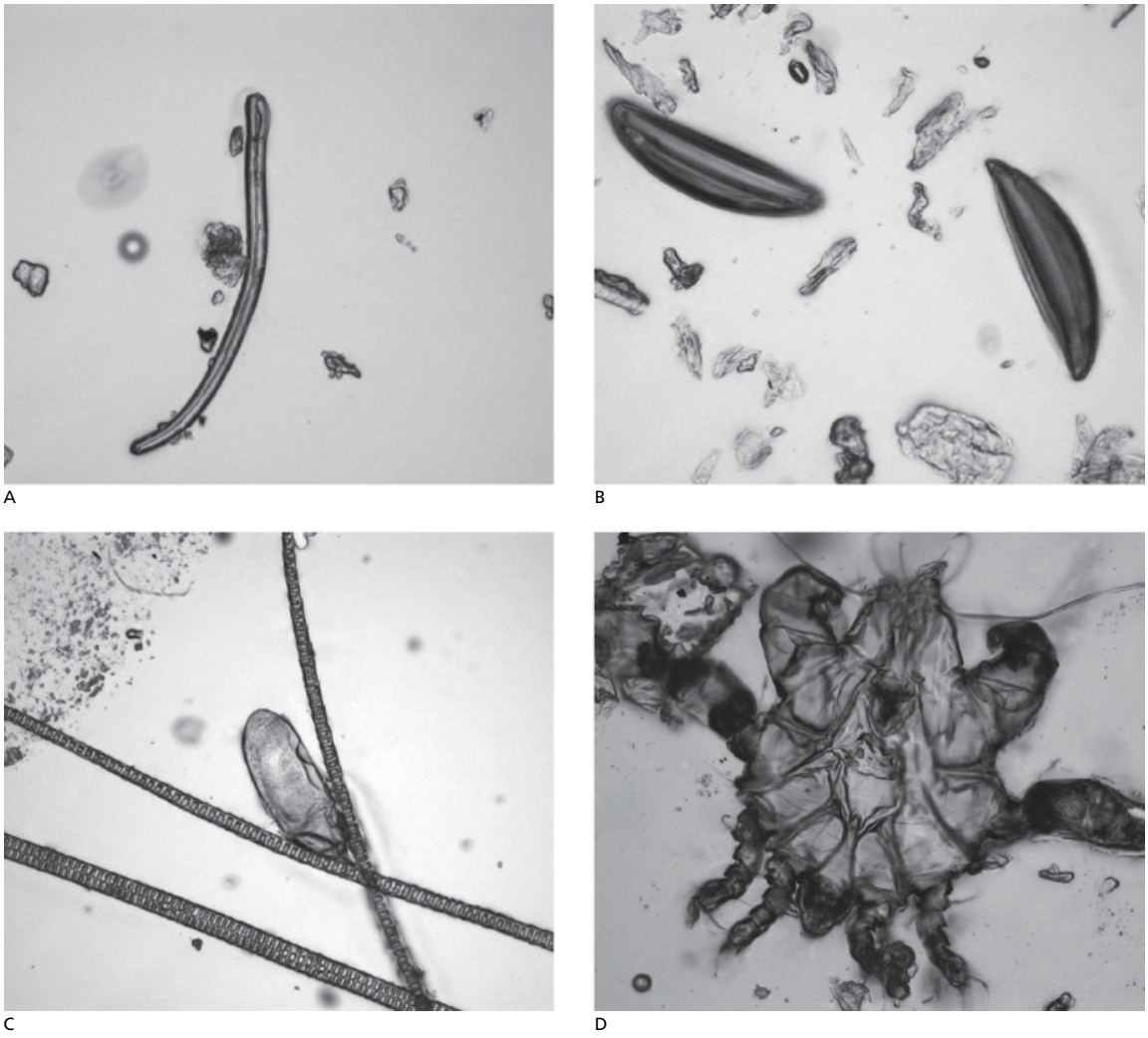


FIGURE 3.68. Photomicrograph demonstrating characteristic appearance of cellophane tape with attached (A) *Syphacia* spp. larval form, (B) *Syphacia* spp. ova, (C) fur mite egg, and (D) fur mite.

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Other Routes

In a research setting, administration of substances into virtually any area of the body may be performed to attain research goals. Anesthesia and surgical exposure of the target organ is often necessary. Intracerebral administration in rodents has been meticulously developed, and requires anesthesia and a stereotaxic unit, which positions the head such that exact coordinates for injection into a specific area of the brain can be performed. In addition to those listed above, routes for research purposes, such as infectious disease models, may include intranasal, intraocular, intra- or transtracheal, intravaginal, intrauterine, intrafetal, or sublingual, to list a few.

Nasolacrimal Duct Flushing in Rabbits

Flushing of the nasolacrimal ducts is performed both as a therapeutic measure and to collect material for diagnostic tests, such as bacterial culture and sensitivity. In most rabbits it can be accomplished using topical anesthesia and restraint in a towel wrap (see Figure 2.11). After allowing sufficient time for the anesthetic to take effect, a lubricated 22- to 26-gauge intravenous catheter (without stylet), or the largest size possible, is introduced into the single punctum by pulling the lower lid laterally and directing the catheter medially, sliding it several mm into the large slit-like opening at the fornix. If resistance to fluid instillation is met after the catheter has been positioned, the tip has likely come up against the 90° turn the duct makes before continuing down the nose. The catheter should be withdrawn 1–2 mm to allow fluid to travel freely around this corner. Five to 10 mL of warm sterile saline is flushed through the duct to dislodge caseous material, and a sterile Petri dish or other suitable container can be used to collect the material as it exits the nose. Acetylcysteine can be added to the saline to break down obstructive debris. A small amount of ophthalmic ointment containing an antibiotic, such as gentamicin, can be instilled after the saline flush. Care must be taken not to apply too much pressure to obstructed ducts, as rupture of the duct and subsequent abscess formation may occur (see Figure 3.26). If flushing cannot relieve the obstruction, twice daily warm compresses and massage over the rostrum for several days can be performed before attempting the flush again. Appropriate topical and systemic antibiotics and anti-inflammatory agents should be used in conjunction with flushing.

Other Techniques

The cellophane tape test can be used to detect the presence of pinworm eggs in rodents. For this technique, a piece of clear tape is pressed gently against the anus. The tape is affixed to a slide and examined under a microscope for the presence of larvae or ova (Figure 3.68). Only pinworm eggs from *Syphacia* spp. can be detected with this method. The same technique can be used to identify fur mites and their ova.

Many other techniques are used in practice and in research that are beyond the scope of this text. Milk collection, bile duct cannulation, bronchoalveolar lavage, and others are included in the references.

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EUTHANASIA

Euthanasia (from the Greek for "a good death") in veterinary medicine refers to humane killing of an animal. Implied in the term "humane killing" is a rapid transition from sensibility to insensibility and a death that is painless, quick, quiet, and free of fear and distress. In all settings, euthanasia decision-making can be fraught with emotion, and it is essential to fully consider and discuss the animal's quality of life and cumulative suffering to ensure that the best decisions are made with the needs of the animal being foremost.

Euthanasia should be carried out by trained personnel using appropriate methods, substances, and facilities, and in accordance with regional social, ethical, or religious conventions. The method of euthanasia will vary with the age of the animal, the species, number, and the intended post mortem use of the animal or its tissues. Agents and procedures specifically contraindicated in the most current version of the American Veterinary Medical Association's euthanasia guidelines (www.avma.org) should not be used for euthanasia. Additional and significant concerns with euthanasia include adverse stress on human participants (operator and witness effects and esthetics), considerations regarding animal distress or appearance of distress, and effects of the method of euthanasia on postmortem evaluation and intended uses of the animal or its parts.

Those administering euthanasia agents to animals must be aware of potential signs of distress. For small mammal species, these may include distress vocalizations, struggling, attempts at escape, panting, salivation, and urination and defecation. Regardless of the technique used, it is critical to verify animal death following euthanasia. Methods of verifying

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death include cardiac auscultation for lack of heartbeat, exsanguination, use of a physical method following a chemical or gaseous method of euthanasia, or thoracotomy via diaphragm transection.

In research settings, the method of euthanasia selected should be compatible with animal welfare and the goals of the research study. Euthanasia agents may induce various biological and chemical changes, and knowledge of these changes is essential. Sodium pentobarbital may induce congestion of alveolar capillaries, congestive splenomegaly, damage to serosal cells of the liver and pancreas, increased plasma glucose and triglycerides, and increases in certain brain chemicals. Carbon dioxide euthanasia often results in multifocal pulmonary petechiation, perivascular edema of lungs, and occasionally, rupture of small intrathoracic capillaries with subsequent localized hemorrhage. Prolonged exposure to CO_2 may also result in marked serum chemistry alterations and hemolysis of blood samples, which may be important for clinical pathology evaluations. Among physical methods, cervical dislocation leads to trauma and marked cervical hemorrhage, while decapitation often leads to reflex inhalation of blood into bronchioles and alveolar spaces.

Euthanasia of Rabbits

Sodium pentobarbital is an excellent agent for rabbit euthanasia if the drug is administered IV, generally by catheter or butterfly needle into a marginal ear vein. The solution is very irritating and care must be taken to prevent perivascular administration. Prior sedation is considered the standard of practice and facilitates needle or catheter placement, reduces stress, and may also minimize the occurrence of a terminal gasp once the animal is unconscious, which can be unnerving for those present. In companion rabbits, sedation facilitates placement of a catheter with an extension set into the lateral saphenous vein. This allows the owner the ability to feed their rabbit treats or provide comfort during the procedure, should they wish to be present. Intraperitoneal injection can also be used, but it takes longer for death to occur than with IV administration, and there is some concern about peritoneal irritation by this route because of acidity of the barbiturate solution. Sodium pentobarbital is regulated in both Canada and the United States, and accurate controls and usage records must be maintained. Cadavers of rabbits killed by lethal pentobarbital injection must not be donated for feeding of raptors or other animals or rendered for pet food production. Burial should also be avoided to reduce the risk of groundwater contamination or wildlife intoxication if the cadaver is consumed.

Inhalant anesthetics are cost-effective euthanasia agents for rabbits that weigh less than 7 kg. Care must be taken to prevent operator exposure by using an appropriate scavenging system for escaped gases. Sedation is strongly recommended prior to gas exposure to minimize stress and prevent struggling and breath-holding during induction, which may be distressing for the operator/observer. Potassium chloride may be administered IV or by intracardiac injection to animals that are deeply anesthetized to ensure loss of heart function.

Carbon dioxide should only be used as compressed gas in a cylinder with a regulator. The chamber used should be as small as necessary to hold the rabbit and should open from the top because CO_2 is heavier than air. The 2020 AVMA euthanasia guidelines recommend a CO_2 displacement rate of 50–70% of the chamber or cage volume/min. This relatively fast flow rate results in significantly earlier loss of sensibility and death than gradual fill. Premedication with sedatives may reduce stress and potential aversion responses; however, these are rare for meat rabbits. On-farm CO_2 euthanasia is unsuitable for kits less than 10 days of age as exposures can take up to 45 minutes to be effective; however, loss of righting reflex with fast-fill exposures are similar between pre-weaned and growing rabbits. Carbon dioxide leaves no tissue residue and has limited effects on cellular architecture. Great care must be taken to ensure the CO_2-exposed animal is dead, especially if it is a neonate. Depending on the fate of the carcass, decapitation or opening the chest cavity can be performed post-exposure. Care must be taken with large CO_2 chambers to ensure that there is good ventilation to minimize operator exposure to large volumes of CO_2 while bending over to remove the animal from the chamber.

Cervical dislocation or decapitation are considered conditionally acceptable methods in rabbits, typically weighing less than 1 kg. The rabbit's head is held in one hand and the hind limbs in the other hand. The rabbit is stretched and the neck twisted dorsally to separate the first cervical vertebra from the skull. Electrical activity in the brain may continue for a few seconds. Cervical dislocation must be conducted by trained persons and for justifiable reasons, for example, if no chemicals can be used, such as with meat rabbits. Device-assisted cervical dislocation may be used on-farm for larger rabbits up to 3–4 kg in body weight. To minimize operator fatigue, fixed commercially available metal V-shaped devices can be used to restrain the head, while the body and legs are deftly pulled to dislocate the neck. Blood may be inhaled into the tracheal opening with this procedure and create the impression in naive observers that the rabbit had a hemorrhagic disease.

Other methods that may be conditionally acceptable in rabbits but only used with great care involve carbon monoxide exposure or stunning by a single, sharp blow to the central skull bones (this latter method has a high probability of error and other methods should be used preferentially). A nonpenetrating captive bolt system (Zephyr stun gun) is increasingly being used for stunning commercial rabbits on-farm and at abattoirs in parts of the US and Canada.

Materials or methods that should not be used include chloral hydrate, nitrogen or argon gases, captive bolt, or decapitation in rabbits that weigh more than 1 kg. Head only electrical stunning is used in some abattoirs for production rabbits but is reported to have an unacceptable failure rate in many settings and countries, in part due to impedance of current by rabbit

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fur. Rabbits and rodents are sometimes exsanguinated to obtain hyperimmune antisera in research settings. Because of anxiety experienced with hypovolemia, exsanguination should be done only be conducted on previously stunned, deeply sedated, or anesthetized animals.

Euthanasia of Rodents

Inhalant agents recommended for euthanizing rodents are isoflurane and sevoflurane, given in air or oxygen and used in well-vented areas. Because of the prolonged time required for euthanasia with this method and the expense of the inhalant agents, animals may be induced with isoflurane and then switched to carbon dioxide gas exposure, once they are deeply anesthetized. Rodents being euthanatized in chambers should be of the same species, sex, and age, should not be crowded or layered, and should not be wetted with the anesthetic. The chamber should be cleaned before use to minimize odors that may signal distress. Repeated exposure to isoflurane is strongly aversive to mice and rats, and other euthanasia methods may be considered for animals that have undergone isoflurane anesthesia in the past. To protect personnel from waste anesthetic gasses, these procedures must be performed in a well-ventilated area.

Carbon dioxide, with or without premedication with halogenated anesthetics, is an effective and inexpensive euthanasia agent for rodents. The 2020 AVMA euthanasia guidelines recommend a CO_2 displacement rate of 30–70% for laboratory rodents. There appears to be no benefit to combining O_2 with CO_2 for euthanasia because the addition of oxygen slows the anesthesia and induction process. When possible, inhaled agents should be administered under conditions in which animals are most comfortable (e.g., for rodents, in a dark, quiet environment). The animals should be left in the chamber for several minutes until respiration has ceased (i.e., at least 3 minutes for mice 21 days of age and older and at least 10.5 minutes for rats of similar ages). Following this, the animal should be removed and death confirmed with the use of a secondary method, such as cervical dislocation, exsanguination or opening the chest wall, prior to disposal. The practice of immersion, in which conscious rodents are placed directly into a container prefilled with 100% CO_2, is unacceptable.

There is continued controversy as to whether CO_2 inhalation is aversive to small rodents and whether it is humane. Repeated exposures to carbon dioxide inhalation are likely aversive to adult rats and mice, based on avoidance behavior studies. However, aversion seen in single trial euthanasia studies can be difficult to differentiate behaviorally and physiologically from that induced by exposure to isoflurane. This is an area of active and ongoing research, and the acceptability of CO_2 as a euthanasia agent for rodents must continue to be evaluated as new data become available.

Neonatal rodents are resistant to the hypoxia-inducing effects of CO_2 , and alternative methods are recommended (e.g., injection with chemical agents, cervical dislocation, or decapitation with a sharp pair of scissors). If dead rodents or rabbits are to be used to feed other animals (snakes, carnivores, and raptors), euthanasia with CO_2 or cervical dislocation is recommended to avoid secondary poisoning with a euthanasia agent.

IV injections are challenging in rodents so the intraperitoneal approach is used commonly as an alternative. Concentrated barbiturate solutions specifically intended for euthanasia may be irritating when given by the IP route in unsedated animals. The recommended dosage for euthanasia with sodium pentobarbital is 150–200 mg/kg. Care must be taken to ensure that the heart has stopped prior to disposal. Sodium pentobarbital administered IV or IP is an excellent euthanasia agent in sedated animals; however, rodents should be placed in small cages following injection to reduce excitement and injury during anesthetic induction prior to death. Barbiturates are controlled substances and are not available to all animal care personnel.

Cervical dislocation or decapitation is acceptable with conditions in rodents, i.e., may be used with justification and by trained personnel in research settings. While it has the potential to be a rapid and humane killing technique, it is often performed incorrectly, resulting in a prolonged time to death. Cervical dislocation is limited to mice, hamsters, and immature rats (<200 g). To euthanatize small rodents by cervical dislocation, the animal is grasped on the neck at the base of the skull or a rod is placed over the neck at the skull base and the tail is pulled. Dislocation usually occurs in the posterior cervical or thoracic spine.

Rapid freezing by immersion in liquid nitrogen is not acceptable for killing animals unless they are first deeply anesthetized. Carbon monoxide is a euthanasia method that is acceptable with conditions when the conditions for effective and safe use can be met, e.g., this must occur in a well-ventilated area to ensure operator safety. When first exposed, people may experience headache and fatigue. However, with higher concentrations or prolonged exposure, loss of consciousness and cardiorespiratory arrest may occur. Methods not recommended for use in rodents include nitrogen or argon gas inhalation, and cervical dislocation and decapitation of rats weighing 200 g or more.

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Chapter 4

Clinical Signs and Differential Diagnoses

The clinical signs commonly encountered in rabbits and rodents are associated with a variety of conditions involving all major systems. This chapter begins with a general discussion about recognizing signs of illness, including the presence of pain, followed by differential diagnoses for various commonly observed clinical signs organized by species. These diagnostic alternatives are based on published literature as well as the authors' experiences and are not meant to be exhaustive, but rather to cover the most common diseases seen. Additional information, where needed, may be extrapolated from other species or gleaned from the references. Detailed information concerning specific diagnoses may be found through the index, in the species-categorized references in Chapter 5, or in the general reference works listed in Chapters 1 and 2. Diagnosis based on clinical signs alone can be presumptuous and premature, and confirmation is approached by taking a thorough history, conducting a clinical examination, and adjusting the assessment based on the results of further diagnostic testing. A summary of zoonotic conditions affecting rabbits and rodents may be found in Table 4.25 at the end of this chapter. Good hygiene practices including routine hand washing or sanitation after handling any animal should always be promoted in the clinic, institution, home, abattoir, and commercial breeding and retail shop settings to minimize the risk of disease transmission between animals and their human caregivers.

RECOGNIZING SIGNS OF ILLNESS AND PAIN IN RABBITS AND RODENTS

Detecting early signs of illness and pain can be challenging in rabbits and rodents because they are prey species and they are naturally predisposed to mask any signs of being unwell. Even for companion animal owners, early signs of distress and illness may be subtle and difficult to detect such that veterinary consultation is often delayed until animals are in more advanced stages of illness. In research settings, rabbits and rodents are often most relaxed in front of their daily caregivers who are essential for detecting early signs of change. In general, observing changes in behavior and responsiveness, such as hunched posture, decreased activity, playing, and exploration, reduced eating and defecation, increased scratching, and reduced grooming, is an indication that rabbits and rodents may not be feeling well. This should spur more frequent observations to determine whether the animal is stable and the issue is resolving, the animal is stable but the issue is not resolving or the animal's condition is worsening. If either of the latter two are apparent, then a veterinary consultation should be sought without delay. Many conditions and diseases have a good prognosis if caught and treated early while animal condition is stable. Treatment may need to be delayed for small rodents and rabbits who are experiencing clinical deterioration, dehydration, hypothermia, and/or who have experienced significant pain or distress. These small patients may need to be gently rewarmed and rehydrated before further examination and diagnostics are possible.

Pain in small rodents and rabbits is multidimensional and individual, resulting in behavioral and physiologic changes that may manifest slightly differently between animals. Pain assessment can also be affected by the location and nature, duration and intensity of the stimulus. Pain pathways are near identical across mammal species, and we should assume that treatments, procedures, and conditions that are painful in people are also painful in small rodents and rabbits and thus provide appropriate care and treatment. The inability of people to recognize pain in small rodents and rabbits does not mean it is not present. Specific details on provision of pharmacologic and nonpharmacologic support for small rodents and rabbits may be found in Chapter 3.

For practical purposes, the most sensitive indicators of pain tend to be behavioral. Ideally, animals are observed indirectly—either across a row in a barn, through a ward or housing room window in a clinic or research setting, or across the room in a

Harkness and Wagner's: Biology and Medicine of Rabbits and Rodents, Sixth Edition. Patricia V. Turner, Colette L. Wheler, Hugues Beaufrère, Niora Fabian, and John E. Harkness.
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FIGURE 4.1. The hunched and withdrawn posture and behavior of this rabbit is consistent with pain. Courtesy of Calgary Avian & Exotic Pet Clinic.

home setting (Figure 4.1). More time spent observing by someone familiar with the specific animal will often improve the accuracy of the assessment. Many changes in clinical condition are not specific to pain, including squinting of the eyes, hunched posture, piloerection, a poor hair coat, and reduced grooming, altered or subtle changes in activity, exploration, and locomotion, reduced food intake and feces production, and teeth grinding. These signs may be used as part of the weight of evidence to determine that animals are unwell and potentially in pain. Animals limping, guarding a limb, or with an open wound or ulcer may be safely assumed to be in pain. Mice, rats, and rabbits experiencing acute pain following castration or laparotomies may demonstrate belly pressing on the floor or cage bottom, frequent back arching and yawning, or abdominal writhing (i.e., muscle spasms seen in the flank area).

Over the past decade or more, similarities have been determined in facial expressions of different mammals experiencing acute pain, and these have been simplified into tools referred to as facial grimace scores. In animals, pain grimacing typically presents as orbital and cheek tightening (demonstrated by a nose bulge and pulling back of the whiskers and a closing of the eyes) and a backward position of the ears. There are gradations of response dependent on the degree of pain (see Figures 4.2–4.4). Grimace scores have been developed and validated for mice, rats, and rabbits. Accuracy of scoring improves with training and practice, and it is essential to view small rodents and rabbits indirectly when using facial grimace scoring. Facial grimace scores can be influenced by sedation and anesthesia, and treatments should be taken into consideration when scoring. Increasingly, behavioral indicators are combined with facial grimace scoring to improve sensitivity and specificity of pain detection in small rodents and rabbits.

Regardless of whether animals are on-farm, in a pet shop, kept as companions or worked with in research, it is unethical and inhumane to permit small rodents and rabbits to experience prolonged severe pain, suffering, and distress. If pain cannot be adequately managed and appropriately treated on-farm, at home or in the clinic or research setting then animals should be humanely killed (see Chapter 3 for a discussion of end-of-life decision-making and euthanasia).

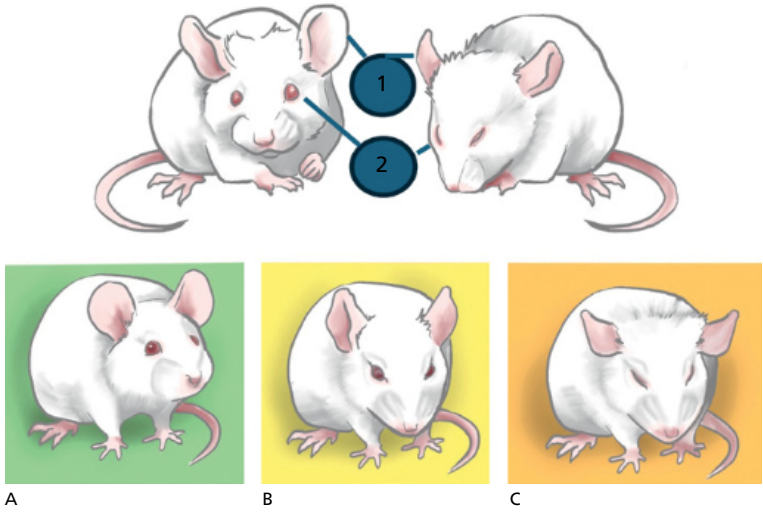


FIGURE 4.2. Simplified facial grimace scoring for pain—Mouse. Body posture, ear position (upright vs flattened back; 1) and squinting or closure of eyes (2) can be used to assess the presence of pain and need for analgesia. The interpretation of the lower row of images is as follows: A: no pain, normal; B: mild pain, observe for improvement or worsening of signs; and C: moderate-to-severe pain, treat with analgesia. Illustration by K. Sokolowski.

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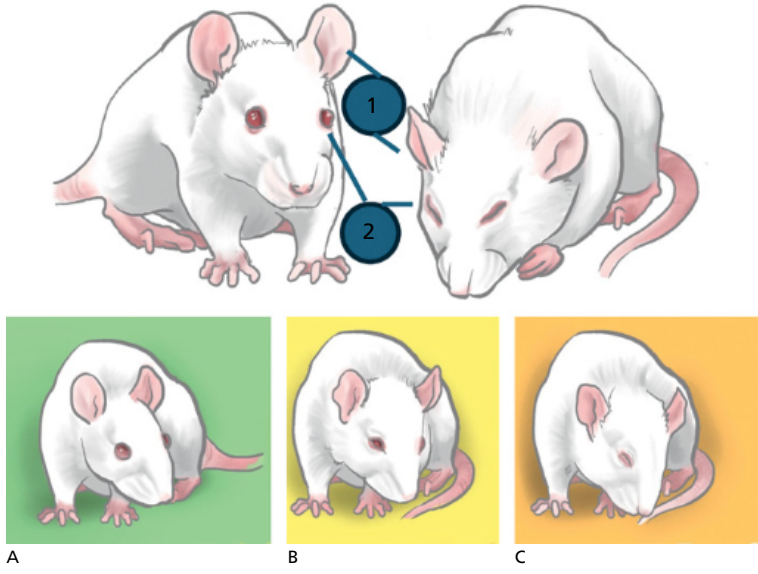


FIGURE 4.3. Simplified facial grimace scoring for pain—Rat. Body posture, ear position (upright vs flattened back; 1) and squinting or closure of eyes (2) can be used to assess the presence of pain and need for analgesia. The interpretation of the lower row of images is as follows: A: no pain, normal; B: mild pain, observe for improvement or worsening of signs; and C: moderate-to-severe pain, treat with analgesia. Illustration by K. Sokolowski.

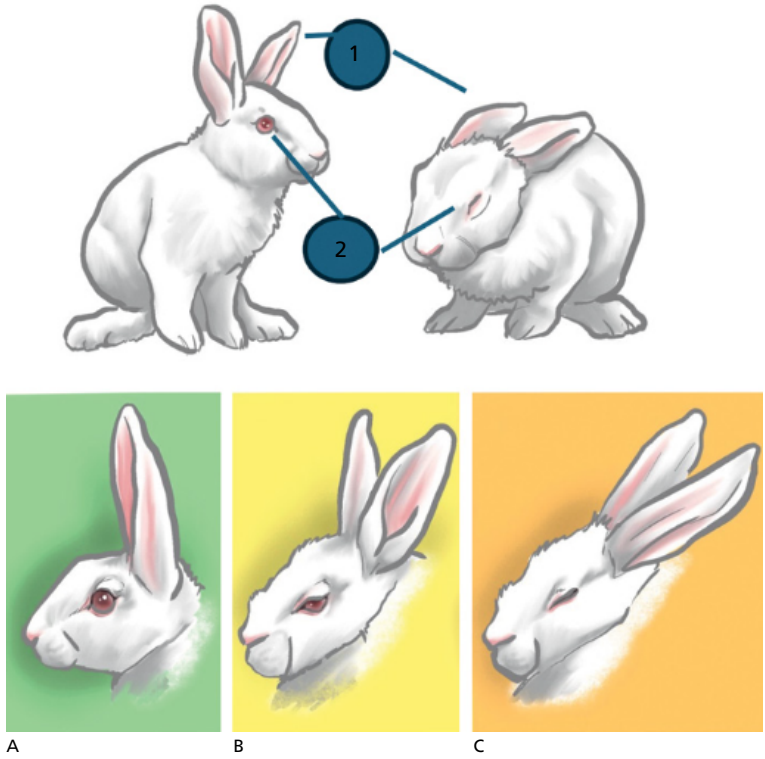


FIGURE 4.4. Simplified facial grimace scoring for pain—Rabbit. Body posture, ear position (upright vs flattened back; 1) and squinting or closure of eyes (2) can be used to assess the presence of pain and need for analgesia. The interpretation of the lower row of images is as follows: A: no pain, normal; B: mild pain, observe for improvement or worsening of signs; and C: moderate-to-severe pain, treat with analgesia. Illustration by K. Sokolowski.

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THE RABBIT

Skin Conditions

As for many small mammal species, rabbits are prized for their soft fur and beautiful coat. Skin problems are readily observed by owners, and although they rarely cause serious disease or death, they are one of the most common presenting signs in clinical practice. A list of infectious and noninfectious differential diagnoses may be found in Table 4.1.

Alopecia

Hair loss or thinning in rabbits may be caused by hormonally induced hair pulling for nests in pregnant or pseudopregnant does, hair chewing related to boredom or stereotypy, overgrooming of self or another (barbering), dietary insufficiency (e.g., fiber deficiency), or ectoparasitism, most commonly *Cheyletiella parasitovorax* infection (back or face). Hair may be inadvertently pulled out more readily with malocclucded or broken incisors, emphasizing that teeth should always be examined. Demodectic and sarcoptic mites are typically associated with pruritus and dermatitis. Less common conditions are mechanical hair loss from rubbing on the cage or feeder, dermatophyte infection, and hair pulling by other house pets or humans. Seasonal molting may also produce hair coat irregularities and thinning, although molting is rarely a cause of alopecia. Hereditary causes of hairlessness exist, including genetically furless strains. Alopecia may develop after several weeks of antiviral or anticancer therapy in rabbits and has been reported following treatment with ribavirin and doxycycline. Temporary patchy alopecia, known as telogen effluvium, may be caused by stress and systemic disease.

Swellings and Masses

Single or multiple subcutaneous masses in rabbits are commonly due to abscesses caused by *Pasteurella multocida* or *Staphylococcus aureus* infection, although other bacteria such as *Yersinia pestis* (cutaneous plague, in areas where the bacteria are endemic), *Fusobacterium necrophorum* (Schmorl's disease), and *Pseudomonas aeruginosa* (wet dewlap disease) may be sporadically involved (Figure 4.5). Swellings related to odontogenic (tooth-related) abscesses may be seen along the jawline or on the face and are frequently polymicrobial with anaerobic bacteria predominating. Mammary gland dysplasia has been reported secondary to pituitary adenoma in the rabbit. Neoplasia (fibromas, osteosarcomas, myxomas, epitheliotropic lymphoma, papillomas), hematomas, cysts, nonspecific granulomas, myiasis from subcutaneous *Cuterebra* spp. larval encystment, diseased mammary glands (e.g., mastitis), and *Coenurus serialis* (*Taenia* spp.) cysts are other causes of cutaneous swellings and masses. *Cuterebra* larvae (i.e., bot fly larvae) are common in rabbits housed outdoors, and they create subcutaneous swellings, often in the dorsal neck area, that encapsulate a single larva with a breathing hole visible at the skin surface. Treatment requires surgical removal of the larva without crushing to avoid anaphylaxis.

Dermatitis

Inflammation of the skin, variably indicated by erythema, alopecia, scaliness, crusting, seborrhea, or ulceration, can be caused by any of several noninfectious causes and infectious agents. Chemical or electrical burns and toxicoses

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Table 4.1. Common presenting skin conditions and differential diagnoses in rabbits.

Condition	Differential Diagnoses
Alopecia	Noninfectious
	Pregnancy/pseudopregnancy
	Fighting/trauma
	Mechanical, e.g., cage bars, hopper
	Exfoliative dermatosis (Dutch)
	Seasonal molting
	Behavioral stereotypy (barbering)
	Hereditary hairlessness
	Drug therapy, e.g., antivirals, anticancer therapies
	Dietary deficiency, e.g., low fiber
	Telogen effluvium
	Infectious
	Ectoparasites, e.g., *Cheyletiella* spp, Leporacarus spp.
	Dermatophytosis, e.g., *Trichophyton* spp
Swellings/masses	Noninfectious
	Trauma/hemorrhage
	Cyst
	Neoplasia (fibroma, lymphoma, papilloma)
	Myiasis, e.g., *Cuterebra* spp
	Mammary gland dysplasia (secondary to pituitary adenoma)
	Infectious
	Abscesses (including odontogenic), e.g., *Pasteurella* spp.
	Staphylococcus spp., *Fusobacterium* spp. (Schmorl's disease or necrobacillosis)
	Myxomatosis
	Plague (cutaneous bubos, following *Yersinia pestis* infection; rare)
	Mastitis
Dermatitis	Noninfectious
	Sebaceous adenitis
	Exfoliative dermatitis, e.g., thymoma
	Chemical/electrical burn
	Toxicoses
	Pododermatitis
	Urine scalding
	Ehlers–Danlos syndrome
	Dietary deficiency, e.g., zinc
	Fly or tick bites
	Myiasis
	Infectious
	Viral, e.g., myxomatosis
	Bacterial, e.g., *Streptococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp. (wet dewlap disease/moist dermatitis), *Treponema cuniculi* (rabbit syphilis)
	Yeast infections, e.g., *Malassezia* dermatitis
	Dermatophytosis, e.g., *Trichophyton* spp., *Microsporum* spp.
	Parasitic, e.g., fleas, *Psoroptes cuniculi* (ear mites), pediculosis, scabies, *Notoedres* spp., *Cheyletiella* spp., *Demodex cuniculi*

should always be considered in rabbits that roam freely in the house. This reinforces the importance of close supervision of rabbits during out-of-enclosure exercise, and forms of exercise permitted is an important question to ask when taking the history. Similarly, a thorough history may rule out the possibility of dietary deficiency. The ear mite, *Psoroptes cuniculi*, causes crust formation and reddening of the outer ear canal, the inner aspect of the pinna, and, in rare

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FIGURE 4.5. Subcutaneous swellings around the site of fracture repair of the tibia in a rabbit caused by *Pasteurella multocida*-induced abscessation.

circumstances, the moist areas of the dewlap or perineum. The mite itself is seen readily under a microscope or by using a hand lens. The fur mite, *C. parasitovorax* (walking dandruff), may cause scaly dandruff accumulations deep in the hair coat with occasional hair loss and oily dermatitis on the face or back. This differs for sarcoptid mites, which are found rarely on the face, ears, and limbs. *Demodex cuniculi* infestation has been reported less commonly in rabbits. *Leporacarus gibbus* may cause scaling, erythema, pruritus, and alopecia and has zoonotic potential. Another common dermatopathy is decubital ulcer formation with pododermatitis (sore hocks; see Chapter 5 for information on scoring lesions). Some rabbits develop a dry necrosis on the plantar surface of one or both hind feet following housing on wire or housing in excessively wet or soiled conditions. This problem may be exacerbated by self-mutilation with secondary bacterial contamination.

Less common causes of dermatopathies include bites by flies; fleas, typically dog or cat fleas such as *Ctenocephalides felis* or *C. canis*; lice such as *Hemodipsus ventricosus*, which may induce anemia; and tick bites (*Hemaphysis leporipalustrus*) in rabbits housed or spending time outdoors. Sebaceous adenitis, urine scalding (especially in obese rabbits), an immune-mediated exfoliative dermatosis of Dutch rabbits, thymoma-induced scaling, and Ehlers–Danlos syndrome have also been reported in rabbits. Sebaceous adenitis may be associated with systemic clinical signs in rabbits.

Bacterial dermatopathies can be caused by several organisms. Infection with *P. aeruginosa* (wet dewlap disease) may be seen in rabbits that play with their water bottles or that are housed in damp unhygienic environments. The condition is characterized by a greenish-blue discoloration of the fur and a distinctive odor. Purulent discharge from rhinitis and conjunctivitis due to *P. multocida* often causes dermatitis of the surrounding skin. Other bacteria infecting the skin include *S. aureus*, *F. necrophorum* (typically infecting wounds), *Actinomyces pyogenes*, and *Treponema paraluiscuniculi* infections of the genitalia and nose. Any moist, ulcerative dermatitis condition can be secondarily infested with maggots (myiasis), particularly in rabbits housed outside. Other causes of dermatopathies in rabbits include dermatophytosis, predominantly from *Trichophyton mentagrophytes* infection. A significant proportion of rabbits may carry this agent subclinically. *Malassezia*-induced dermatitis is uncommon in rabbits.

Gastrointestinal Conditions

Anorexia

Anorectic rabbits, defined as animals who have consumed 25% or less of their normal daily ration for three or more consecutive days or with complete cessation of food ingestion for one or more days, commonly present to practitioners and should be considered a medical emergency and treated aggressively. Rabbits who remain off feed for prolonged periods of a week or more may develop an irreversible fatal fasting condition with a very poor prognosis. Rabbits who are off feed will generally not drink, and fluid assessment and replenishment are appropriate in most cases while trying to determine the underlying cause of anorexia. The most common etiologies of this condition relate to dental disease (sometimes accompanied by ptyalism with a resultant moist chin or dewlap), gastric stasis usually caused by inappropriate low-fiber diets, sudden dietary or management changes, pain from any cause (often accompanied by bruxism), odontogenic abscesses, and systemic disease of any nature (Table 4.2). Other potential causes of anorexia in rabbits include recovery from anesthesia, environmental stress such as increased ambient temperature, insufficient water supply, dehydration from any cause, unpalatable or moldy feed, changed feeding or watering devices, gastric ulceration, gastrointestinal accident such as intussusception or obstruction, loss of olfactory senses secondary to rhinitis, neoplasia, and acidotic or ketotic conditions secondary to hepatic lipidosis.

Although large trichobezoars may be found in the stomach of anorectic rabbits, current thinking is that this hair accumulates secondary to gastric or enteric stasis and that large hair masses rarely are responsible for primary gastric obstructions. In addition, gastrointestinal stasis and anorexia are common in companion rabbits and may be associated with any painful or systemic condition, including urolithiasis, liver lobe torsion, and otitis.

Diarrhea

A specific cause of diarrhea in a rabbit is often difficult to determine. Weanling animals are particularly susceptible to developing diarrhea because the simultaneous change in diet (from a milk-based high-fat and -protein diet to a more fiber-based diet) and concomitant digestive system maturation, stresses of transport, social group changes, and waning of

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Table 4.2. Common presenting gastrointestinal conditions and differential diagnoses in rabbits.

Condition	Differential Diagnoses
Anorexia	Noninfectious
	Dental disease (malocclusion, ptyalism)
	Gastric stasis
	Sudden dietary change
	Insufficient water supply
	Change in husbandry practices (environmental stress)
	Moldy feed
	Oral foreign body
	Gastric/intestinal obstruction
	Intestinal accident
	Gastric ulcers
	Oral papillomatosis
	Pain
	Neoplasia
	Postanesthetic anorexia
	Loss of olfactory sense (secondary to rhinitis)
	Secondary to hepatic lipidosis
	Other diseases or conditions associated with pain and/or abdominal discomfort
	Infectious
	Secondary to gastrointestinal infections (see below) as well as systemic disease, caused by many agents, including rabbit hemorrhagic disease virus type 2 (RHDV2), and leporid herpesvirus-4.
Diarrhea	Noninfectious
	Dietary indiscretion (e.g., carbohydrate overload, excessive young greens)
	Mucoid enteropathy
	Food allergy
	Low-fiber diet
	Inappropriate use of antibiotics (*C. difficile* overgrowth)
	Hepatic lipidosis (pregnancy toxemia)
	Aflatoxicosis
	Infectious
	Viral enteritis, e.g., rotavirus, coronavirus (higher morbidity and mortality), astrovirus
	Bacterial enterocolitis, e.g., *Clostridium spiroforme* (typhlocolitis), *Clostridium piliforme* (Tyzzer's disease), *Lawsonia* spp (proliferative enteritis), *E. coli* (both EPEC and EHEC serotypes), *Salmonella* spp
	Protozoal infection, e.g., coccidiosis (*Eimeria* spp), cryptosporidiosis
	Hepatitis, e.g., coccidiosis (*Eimeria stiedae*), listeriosis (does), tularemia, staphylococcosis
	Parasitic infection (rarely induces diarrhea), e.g., pinworms (*Passalurus ambiguus*; perianal itching), heavy tapeworm larval infestation (may also see abdominal distension)
Constipation	Noninfectious
	Obesity
	Inappropriate diet (low fiber)
	Lack of exercise
	Dysautonomia (grass sickness; rare outside the UK) or cecal impaction
	Anorectal papilloma (nonviral)

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Table 4.2. ***(continued)***

Condition	Differential Diagnoses
Distended abdomen	Noninfectious
	Pregnancy
	Obesity
	Uterine adenocarcinoma
	Hydrometra
	Cardiac disease with ascites
	Gastrointestinal disorders
	Liver lobe torsion
	Urolithiasis
	Infectious
	Hepatic coccidiosis
	Pyometra
	Metritis

maternal antibodies converge to enhance susceptibility to opportunistic pathogens. Fluid assessment and replacement and an assessment of overall hygiene practices are appropriate in all circumstances. In most instances, the definitive diagnosis is multifactorial and complex, involving two or more introduced or resident microorganisms, changes in the intestinal milieu, alterations in management practices, and elaboration of bacterial enterotoxins. Specific examples of such relationships include colibacillosis and coccidial coinfection, clostridial enterotoxemia preceded by Tyzzer's disease (*Clostridium piliforme* infection) or *Lawsonia intracellularis* infection, or rotavirus infection and clostridial enterotoxin elaboration following carbohydrate overload and bacterial overgrowth.

Noninfectious causes of diarrhea include dietary indiscretion (carbohydrate overload or low-fiber diets), aflatoxins in the feed, food allergy, and antibiotic-induced dysbiosis (i.e., iatrogenic) with overgrowth of *C. difficile* and enterotoxin production, mucoid enteropathy, and hepatic lipidosis secondary to pregnancy toxemia or obesity.

Specific infectious causes of diarrhea to consider include rotaviral, astroviral, and coronaviral infections in kits and weanlings, coliform infections in rabbits of all ages, *Clostridium spiroforme* typhlocolitis, *L. intracellularis* ileitis, and *C. piliforme* typhlitis. Protozoal overgrowth by coccidia is very common, while *Cryptosporidium parvum* infections are less common. Endoparasite infestation rarely results in diarrhea. Pinworm infestation (*Passalurus ambiguus*) is common in companion rabbits yet is usually subclinical or presents with mild perianal irritation.

Hepatitis may also present clinically as diarrhea or as abdominal distension and runting in young animals. Common causes of hepatitis include hepatic coccidiosis and hepatitis secondary to systemic bacterial infection, for example, *Staphylococcus* spp., *Listeria monocytogenes*, and *Francisella tularensis*.

Constipation

Obesity, inappropriate diets with high-carbohydrate and low-fiber content, and lack of exercise are the most common causes of constipation in rabbits. Cases of dysautonomia with cecal impaction and degeneration of autonomic neurons are rare and untreatable. Recurrent cecal impaction can lead to the inability to produce normal cecoliths, abdominal pain, and anorexia. Homozygous spotted (English Spot) and Checkered Giant breeds may be predisposed. Anorectal papillomas are not related to virally induced oral papillomas, which are seen in up to 30% of companion rabbits, but because they are friable masses, they may induce mild rectal bleeding if they become ulcerated, leading to obstipation, and associated constipation. Signs resolve readily with surgical removal of the masses.

Abdominal Distension

Intestinal disorders with gas and fluid accumulation, hepatic coccidiosis, metritis, pyometra, uterine adenocarcinomas, hydrometra, pregnancy, cardiac disease with ascites accumulation, and obesity all may cause an enlarged abdomen in rabbits.

Cardiorespiratory Conditions

Nasal Discharge

Serous or mucopurulent rhinitis with sneezing is classically associated with *P. multocida* infection ("snuffles") (Table 4.3). Discharge may also be seen on the forelimbs, as animals attempt to groom themselves. *S. aureus*, *Bordetella bronchiseptica*, and *Neisseria* spp. may also be upper respiratory pathogens in rabbits. Dental disease may result in nasal discharge, especially with overgrowth of premolar or molar tooth reserve crowns (especially upper P2). A nasal discharge may accompany heat stress, allergies to hay or feed dust, nasal foreign bodies, neoplasia, fungal abscesses, myxomatosis, and rabbit pox. Myxomatosis is a deadly but rare viral condition of

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Table 4.3. Common presenting cardiorespiratory conditions and differential diagnoses in rabbits.

Condition	Differential Diagnoses
Nasal discharge/ rhinitis/sneezing	Noninfectious Dental disease (premolar and molar reserve crown elongation) Allergy (dust, hay) Increased temperature Nasal foreign body Neoplasia Infectious *Pasteurella multocida* Other bacterial infections, e.g., *Staphylococcus aureus, Bordetella bronchiseptica, Neisseria* spp Fungal infection, e.g., *Aspergillus* spp Rabbit pox Myxomatosis
Dyspnea	Noninfectious Primary cardiac disease (pulmonary edema, pleural effusion) Anesthetic-induced myocardial necrosis Stress Toxic, e.g., avocado leaf ingestion Foreign body Aspiration Chylothorax Tracheal stenosis Neoplasia, e.g., lymphoma, thymoma, pulmonary metastases of uterine adenocarcinoma Infectious Bacterial pneumonia, e.g., *P. multocida, S. aureus, Klebsiella pneumoniae, B. bronchiseptica* Viral infection, e.g., rabbit hemorrhagic disease virus-2 (calicivirus), leporid herpesvirus-4 infection

rabbits in most areas of the world except California, Australia, and parts of Europe and Brazil, where it has become enzootic with less serious manifestations in certain wild rabbit populations. Affected animals may initially present with serous or mucous nasal discharge but rapidly develop other signs such as subcutaneous edema and swellings, fever, and depression, suggestive of severe systemic illness.

Dyspnea

As rabbits are obligate nasal breathers, any disease obstructing the nasal cavities and the nasopharynx may lead to dyspnea. Common nasal conditions include bacterial rhinitis, odontogenic rhinitis, and nasal foreign bodies. Labored breathing is often associated with chronic pneumonia caused by *P. multocida.* Other bacterial infections, caused by agents such as *S. aureus, B. bronchiseptica*, and *Klebsiella pneumoniae*, may contribute to disease pathogenesis. Dyspnea may also occur with various viral infections, such as calicivirus (rabbit hemorrhagic disease) or rabbit herpesvirus infection. Tracheal foreign body, aspiration, and toxicity secondary to avocado leaf ingestion with resultant pulmonary edema have also been reported. Tracheal stenosis may occur in rabbits following endotracheal intubation, leading to stertorous respiration. In addition, administration of alpha-2 agonists for anesthesia has resulted in myocardial necrosis, pulmonary edema with resultant dyspnea, and death, likely due to profound hypoxemia. These injectable anesthetic agents can be used safely in rabbits if supplemental oxygen is provided. Dyspnea with sudden death may occur in stressed rabbits and is thought to be due to coronary artery vasoconstriction following sudden catecholamine release. As companion rabbits receive better care and live to older ages, primary heart disease is an increasingly common diagnosis. Dyspnea may result from pulmonary edema or pleural effusions secondary to heart failure, most commonly due to dilated cardiomyopathy. Neoplasia that results in chylothorax (e.g., rare cases of thymoma) and mediastinal masses interfering with respiration

(e.g., thymoma, lymphosarcoma) or that reduce pulmonary capacity (e.g., thymoma, metastatic uterine adenocarcinoma) may also result in dyspnea. Pneumonia and cardiac disease in rabbits usually result in sudden death, but careful ante mortem examination may reveal cyanosis (blue discoloration) of the iris, mucosa, and ears (especially in albino animals), weight loss, depression, and respiratory difficulties.

Endocrine Conditions

Endocrine disease is extremely uncommon in rabbits. Pseudopregnancy may occur following a sterile or unsuccessful mating; however, this is a normal condition that resolves spontaneously between 2 and 3 weeks following breeding. Diabetes mellitus has been reported in New Zealand white rabbits, as has mammary dysplasia secondary to a prolactin-secreting pituitary adenoma. Thyroid disorders, especially hypothyroidism, are also increasingly being recognized in companion rabbits. Adrenal gland disease (atypical Cushing's) can also be seen in rabbits and typically manifests as a return to sexual behaviors in a neutered animal with accompanying weight loss.

Yellow Fat

The occasional presence of distinctive yellow fat in rabbits is caused by a homozygous recessive condition that results in a failure to metabolize xanthophylls. The accumulation of xanthophylls has no deleterious effect on rabbits.

Nervous and Musculoskeletal Conditions

Signs of neuromuscular disease are commonly seen in companion rabbits (Table 4.4). A complete neurologic exam is recommended to localize the lesion; however, signs may be difficult to interpret as not every animal may respond as expected because of stress or species-specific variation (e.g., rabbits lack a menace reflex). Note that the rabbit has no cauda equina and the spinal cord extends the length of the vertebral canal.

Head Tilt/Torticollis/Vestibular Syndromes

Head tilt or wry neck (Figure 4.6) is due in many cases to an otitis media/interna caused by bacteria (sometimes due to *P. multocida* in commercial meat rabbits but often undetermined in companion rabbits) either extending from the pharynx via the eustachian tubes or extending from an otitis externa. Lop-eared rabbits are especially prone to external and medial/internal otitis. At times, no specific middle ear lesions are detected with radiographs or CT and other potential causes of a central vestibular syndrome may include trauma, toxin ingestion (e.g., lead paint ingestion), cerebral larval migrans following exposure to embryonated *Baylisascaris* spp. eggs, toxoplasmosis, encephalitozoonosis (*E. cuniculi*), or neoplasia. Extension of an ear mite infestation from the external ear to the middle ear is uncommon, and in any case such an invasion would be complicated by bacterial infection.

Seizure and Depression

Encephalopathies with resultant seizures or depression may result from bacterial infections or abscesses (e.g., *P. multocida*, *L. monocytogenes*, *S. aureus*), herpesvirus infections (rabbit-specific herpesviruses as well as human herpes simplex viruses), encephalitozoonosis, and cerebral migration by *Baylisascaris* spp. larvae. Severe systemic disease of any form may result in depression or seizures, for example, terminal septicemia and pregnancy toxemia. Other less common causes of seizures include various toxins (e.g., lead), hypoxia, heat stroke, neoplasia, hypoglycemia, idiopathic epilepsy of blue-eyed white rabbits, and vitamin A deficiency. Rabies virus infections of rabbits have been reported in animals with access to the outdoors, generally following raccoon attacks, but are very uncommon.

Incoordination, Paresis, and Paralysis

Incoordination, weakness, and paralysis are commonly caused by vertebral or limb injury. If rabbits are dropped, allowed to thrash about during restraint, or become excited in a cage with limited space, they may fracture the lower spine and damage the spinal cord, because of their high muscle-to bone ratio. The degree and duration of the resulting paresis or paralysis and loss of bladder and sphincter control depend on the severity and location of the cord lesion. Hindlimb paralysis with loss of deep pain sensation always carries a poor prognosis. Other causes of incoordination and paresis include muscular dystrophy secondary to nutritional deficiencies (vitamin A, E, or selenium), cerebrospinal nematodiasis, cerebrovascular accident, encephalitozoonosis, otitis interna, bacterial encephalitis, insecticide poisoning, pregnancy toxemia, anemia secondary to blood loss, severe inanition, heat exhaustion, spinal abscess or neoplasia, spondylosis or spondylitis, and osteoarthritis. Rare conditions include rabies virus infection, magnesium deficiency, congenital splayleg, and several other rare inherited musculoskeletal conditions. Splayleg, or the inability to adduct one or more limbs secondary to developmental deformities of the joints and muscles, has also been attributed to the presence of a smooth flooring surface during postnatal development.

Ocular Conditions

Conjunctivitis and Dacryocystitis

Conjunctivitis and dacryocystitis with or without corneal damage caused by *P. multocida* infection occur commonly and may be associated with a mucopurulent discharge. Dacryocystitis may also arise secondary to blockage of the lacrimal duct by dental abscesses or maxillary cheek tooth reserve crown elongation. Other bacteria, *Chlamydophila* spp., dust or other foreign matter in the eye, trauma, dystichiasis, trichiasis (especially in French Rex), and rabbit pox also may cause an ocular discharge and irritation of the conjunctiva. Corneal ulceration secondary to trauma is a common sequela of bacterial conjunctivitis and exposure keratitis secondary to exophthalmos is also common in companion

Table 4.4. Common presenting nervous and musculoskeletal conditions and differential diagnoses in rabbits.

Condition	Differential Diagnoses
Head tilt/torticollis	Noninfectious
	Trauma
	Cerebral larval migrans, e.g., *Baylisascaris* spp
	Cerebrovascular accident
	Peripheral vestibular disease
	Toxins, e.g., lead (paint)
	Neoplasia, e.g., pituitary adenoma
	Infectious
	Otitis media/interna secondary to bacterial infection
	Brain abscess
	Severe otitis externa, e.g., *P. cuniculi*
	Toxoplasmosis
	Encephalitozoonosis
Seizures	Noninfectious
	Pregnancy toxemia
	Cerebral larval migrans
	Heat stroke
	Toxins, e.g., lead (paint)
	Hypoxia
	Hypovitaminosis A
	Severe systemic disease, e.g., rabbit hemorrhagic disease, terminal sepsis
	Idiopathic epilepsy
	Neoplasia Infectious
	Bacterial encephalitis/meningitis/abscess, e.g., *P. multocida, Listeria monocytogenes, S. aureus, Streptococcus* spp
	Encephalitozoonosis
	Viral infection, e.g., herpesvirus encephalitis, rabies virus
	Metabolic (e.g., hypoglycemia)
Paresis/paralysis	Noninfectious
	Trauma (leg/muscle)
	Vertebral fracture
	Scoliosis
	Splayleg (congenital or acquired)
	Spondylosis/spondylitis
	Osteoarthritis
	Spinal neoplasia
	Severe anemia, e.g., secondary to blood loss
	Severe inanition
	Intervertebral disk disease
	Hypovitaminosis E/selenium deficiency
	Hypovitaminosis A
	Toxicity, e.g., lead, insecticide
	Cerebrovascular accident
	Infectious
	Spinal abscess
	Encephalitozoonosis
	Toxoplasmosis
	Rabies virus
	Bacterial encephalitis



FIGURE 4.6. Torticollis is a common presenting sign in rabbits and may be caused by several etiologies. Courtesy of Calgary Avian & Exotic Pet Clinic.



FIGURE 4.7. Congenital unilateral buphthalmia in a New Zealand white rabbit.

rabbits. Exudate and infection from the conjunctiva may spread over the face and under the chin. If *Pseudomonas* spp. infection is involved, fur adjacent to the lesion may be stained blue-green.

Blepharitis

Dry, crusty scabs adhering to the orbital skin and mucous membranes may be caused by *T. paraluiscuniculi*, the agent of rabbit venereal spirochetosis. Accompanying lesions may occur on the genitalia and nose. *P. multocida and S. aureus* infection also may induce blepharoconjunctivitis. Myxomatosis is so far largely confined geographically to the west coast of the US, Mexico, Europe, Australia, and some other areas, where it is enzootic. The disease may involve generalized or nodular swelling of the eyelids, along with a thick mucus discharge. Other eyelid conditions seen occasionally include ectropion and entropion, and trauma associated with fighting.

Exopthalmos

Bulging of a rabbit's eye unilaterally or bilaterally may occur with retrobulbar abscess, as a self-limiting sequela to indwelling external jugular catheters or cervical restraint, or with buphthalmia (Figure 4.7). Other reported causes of unilateral exophthalmos include the presence of *Taenia serialis* coenurus, orbital neoplasia, cellulitis, retrobulbar fat prolapse, and salivary mucocele. Bilateral periodic exophthalmos has been associated with mediastinal masses such as thymoma or lymphoma. Primary ocular neoplasms are rare in rabbits.

Other Conditions

Cyclopia, lens or optic disc coloboma, corneal dystrophy, heritable cataracts, cataracts and uveitis following *Encephalitozoon* spp. infection in dwarf breeds (phacoclastic uveitis), conjunctival overgrowth (pseudopterygium), persistent hyperplastic primary vitreous, corneal dermoids, lipid keratopathy, and deep glandular hyperplasia of the nictitating membrane (cherry eye) are ophthalmic problems seen less commonly. Entropion and ectropion have been reported and can be surgically corrected.

Genitourinary Conditions

Increased water intake and urination by rabbits accompany lactation, heat stress, febrile disease, dry feed, salty diets, renal disease, and enteritis (Table 4.5). Potable water must be provided to rabbits at all times. Absorption of calcium by rabbits is not as well controlled by vitamin D, parathyroid hormone, and estrogen as for other species. Serum calcium levels in rabbits are directly proportional to calcium levels in the diet and may fluctuate widely. In addition, the urinary fractional excretion of calcium is high in rabbits, around 45–50%. The result is that 50% or more of ingested dietary calcium is excreted in the urine and the end-product may be somewhat thick, cream-colored, or contain mineral debris, and porphyrin (reddish) pigments.

Hematuria

Normal rabbit urine can be pale yellow to red-orange to brown, may vary from clear to opaque, and can resemble pus or blood. Many cases of "bloody" urine turn out to be normal porphyrin-pigmented urine. In addition, blood in the urine must be distinguished from blood originating from the reproductive tract. If the urine contains blood, then bacterial cystitis, urinary bladder polyps, pyelonephritis, renal infarcts, urolithiasis, disseminated intravascular coagulation (DIC), and leptospirosis should be considered. Hemorrhage or bloody discharge from the reproductive tract may occur with ruptured endometrial aneurysms, ulcerated uterine adenocarcinoma, pyometra, or abortion.

Other Renal or Urinary Conditions

Chronic renal failure with increased drinking and urination, secondary to inappropriate diet and an elevated Ca : P ratio, is common in older rabbits. Inappropriate vitamin D supplementation

Table 4.5. Common presenting genitourinary conditions and differential diagnoses in rabbits.

Condition	Differential Diagnoses
Renal conditions	Noninfectious
	Urolithiasis
	Chronic renal failure
	Hypervitaminosis D (dystrophic mineralization)
	Hydronephrosis
	Renal agenesis
	Toxicoses, e.g., gentamycin, Telazol®, NSAIDs, dietary mycotoxins
	Renal cysts
	Bladder polyps
	Fatty infiltration (pregnancy toxemia)
	Neoplasia, e.g., lymphoma, embryonal nephroma (Wilm's tumor)
	Infectious
	Pyelonephritis/nephritis/cystitis secondary to bacterial infection, e.g., *P. multocida, S. aureus, E. coli*
	Renal abscess
	Encephalitozoonosis
Uterine conditions	Noninfectious
	Cystic endometrial hyperplasia
	Pregnancy toxemia
	Infertility, e.g., inadequate protein, hypovitaminosis A, D, E, or hypervitaminosis A
	Abortion, e.g., stress, hyperthermia, trauma
	Uterine torsion
	Uterine/vaginal prolapse
	Endometrial venous aneurysms
	Hydrometra
	Neoplasia, e.g., uterine adenocarcinoma
	Infectious
	Pyometra/metritis following bacterial infection, e.g., *P. multocida, S. aureus*
	Listeriosis (abortion)
	Vulvitis, e.g., *T. cuniculi*
Mammary gland conditions	Noninfectious
	Mammary gland hyperplasia/dysplasia
	Agalactia
	Neoplasia
	Infectious
	Mastitis, e.g., *S. aureus*
Male reproductive conditions	Noninfectious
	Intestinal herniation and strangulation post castration
	Trauma
	Interbuck fighting with testicular evisceration
	Neoplasia
	Infectious
	Orchitis and epididymitis following *P. multocida, Brucella* spp, or *T. cuniculi* infection

with dystrophic mineralization of the kidney can also occur. Acute renal failure following gentamicin, some nonsteroidal antiinflammatory medications (particularly with concurrent dehydration or chronic administration), or Telazol® administration has been reported in rabbits. Less common causes of renal disease include various congenital abnormalities (e.g., cyst, hydronephrosis, and renal agenesis) and fatty infiltration of the kidney in obese animals. Renal tumors are relatively common, including lymphoma and embryonal nephroma (Wilm's tumor). Hypothyroidism has been associated with increased frequency of urination (pollakiuria) in companion rabbits.

Vaginal Discharge

The source and nature of a suspected discharge should be determined to distinguish it from normal urine, which may be red-tinged due to porphyrin secretion, and pasty due to its high mineral content. Uterine adenocarcinomas and uterine venous aneurysms may result in a bloody discharge. Purulent discharge may be caused by *P. multocida* or *S. aureus* infection. A bloody discharge may be associated with recent abortion. Both prolapsed vagina and uterus have been reported.

Infertility

Infertility in rabbits is difficult to diagnose. Factors that may contribute to a real or apparent infertility in animals of either sex are immaturity or senescence of the buck or doe, heat stress, caloric or other nutritional imbalances, such as low-protein diets, hypovitaminosis A, D, or E, or hypervitaminosis A. Other conditions contributing to infertility include overcrowding, overuse of bucks for breeding, autumnal breeding depression, an incompatible mate, estrogenic stimulation, uterine infection (*Chlamydophila* spp., *Listeria* spp., *S. aureus, Moraxella* spp., *P. multocida, Brucella* spp., *Salmonella* spp), uterine venous aneurysms or neoplasia, orchitis, venereal spirochetosis, excessive noise, and retained placentas.

Prenatal Mortality

Resorption, abortion, and stillbirths occur at different times of gestation; however, the causes of fetal loss may be similar. The more common causes of fetal loss are metritis due to listeriosis, pasteurellosis or other bacterial infections, excessively large litters, pregnancy toxemia, inadequate caloric intake, and other nutritional imbalances (see above). Less frequent causes of prenatal mortality include arsanilic acid poisoning, DDT poisoning, congenital abnormalities, heat stress, systemic disease, overcrowding, and nitrate toxicity.

Postnatal Mortality of Kits

There are a number of noninfectious causes of perinatal mortality of kits. Maternal inexperience, handling of kits or disturbing the nest, inadvertent cannibalism during consumption of the placenta, insufficient nest material, excessive noise or external disturbances, deformed, chilled, or injured young, lack of access of the dam to adequate water or food supplies, aspiration pneumonia, caloric deficiency, vitamin A excess in the doe, young animals that have fallen out of the nest, and agalactia can all lead to neonatal neglect or death. Agalactia can result from gastrointestinal stasis, malocclusion, anorexia, mastitis, or restricted access to water.

Death of young rabbits can also be caused by enterotoxemia (*Escherichia coli*), trampling, enteropathies, peracute *P. multocida* septicemia, starvation or dehydration, pyloric stenosis, and ingestion of quaternary ammonium residues. Young may die after suckling a doe with staphylococcal mastitis.

Sudden Death

Sick rabbits can be very fragile, and handling and examination should be gentle and may need to occur in stages. Death of mature rabbits with few or no preceding signs is a common problem. This situation may occur with acute stress, acute or chronic bacterial pneumonia and disease (especially pasteurellosis), heat stress, enterotoxemia, coliform infections, underlying heart disease, dehydration, electrocution (from electrical cord chewing), intoxications, and ketoacidosis (pregnancy toxemia). The death of does when the litter is a few weeks old is most likely a result of toxemia caused by *Clostridium* spp. or the consequence of retained placenta(s).

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THE GUINEA PIG

Skin Conditions

Alopecia

A number of causes for hair loss exist in the guinea pig including hereditary hairlessness in breeds that have become popular in recent years (e.g., Skinny pigs) (Table 4.6). Hair loss, thinning, or failure of hair to grow may occur in intensively bred sows, particularly in the last trimester of pregnancy when metabolic demands are considerable. Sows that are repeatedly bred lose increasing amounts of hair with successive pregnancies and lactations due to hormonal changes. Hair loss or growth depression is seen also in young pigs near weaning age, in older sows with follicular ovarian cysts, and in animals that consume protein-deficient feed (usually less than 15% crude protein) or other nutritionally deficient diets, such as those with inadequate vitamin C or zinc levels. Guinea pigs often barber one another and younger animals approaching sexual maturity may fight, resulting in hair loss and bite wounds. Abrasion on rough surfaces, such as feeders, fungal infections (*T. mentagrophytes, T. benhamiae*), acariasis (*Trixacarus caviae*), and certain drug therapies may also result in hair loss.

Swellings and Masses

Subcutaneous abscesses are common in guinea pigs. *Streptococcus zooepidemicus* (cervical lymphadenopathy or "lumps") and *S. aureus* ("bumblefoot" or chronic pododermatitis with little pus accumulation) infections are common. *S. aureus* – induced mastitis also is seen. *Caviibacter abscessus* and *Yersinia pseudotuberculosis* also may induce abscesses. Submandibular abscesses are frequently caused by odontogenic infections (Figure 4.8). Neoplasia is rare in

Table 4.6. Common presenting skin conditions and differential diagnoses in guinea pigs and chinchillas[a].

Condition	Differential Diagnoses
Alopecia	Noninfectious
	Fighting/trauma[a]
	Mechanical, e.g., feeder[a]
	Behavioral stereotypy (barbering)[a]
	Hereditary hairlessness (Skinny pig and other naked varieties)
	Follicular ovarian cysts, (endocrinopathy)
	Late pregnancy
	Drug therapy, e.g., anticancer therapies
	Nutritional deficiencies, e.g., zinc, hypovitaminosis C
	Infectious
	Dermatophytosis,[a] e.g., *Trichophyton* spp.
Swellings/masses	Noninfectious
	Trauma/hemorrhage[a]
	Neoplasia (fibrosarcoma, lymphoma, mammary adenocarcinoma, trichofolliculoma, cavian leukemia with lymphadenopathy, thyroid carcinoma)
	Infectious
	Cervical lymphadenitis or subcutaneous abscesses[a] (*Streptococcus equi* subspecies *zooepidemicus*)
	Abscesses and odontogenic infections,[a] e.g., *Staphylococcus* spp, *Yersinia pseudotuberculosis*
	Mastitis
Dermatitis	Noninfectious
	Fighting/bite wounds[a]
	Contact allergy
	Pododermatitis
	Nutritional deficiencies, e.g., hypovitaminosis C
	Urine scalding[a]s
	Infectious
	Bacterial,[a] e.g., *Streptococcus* spp., *Staphylococcus* spp.
	Yeast, e.g., *Malassezia* dermatitis
	Dermatophytosis, e.g., *Trichophyton* spp.
	Parasitic, e.g., fleas (*Ctenocephalides felis*), fur mites (*Chirodiscoides caviae, Demodex caviae*), sarcoptic mange (*Trixacarus caviae*), pediculosis (*Gyropus ovalis, Gliricola porcelli*), myiasis

[a] Denotes conditions that may also occur in chinchillas.

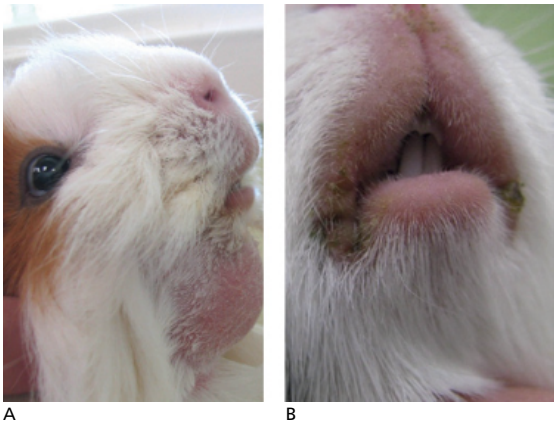
guinea pigs but epithelial tumors seen include trichofolliculoma and mammary adenocarcinoma as well as fibrosarcoma, lymphoma, and a retrovirus-induced cavian leukemia with associated lymphadenopathy. Thyroid masses are readily palpable in guinea pigs and may be due to hyperthyroidism or thyroid gland tumors. Long-haired guinea pigs often develop a large mat of hair gummed together with waxy secretions from the supracaudal perianal gland at the base of the spine, which is occasionally mistaken for a tumor. The gland is testosterone-sensitive and occasionally hypertrophies in intact males.

Rough Hair Coat

Abyssinian guinea pigs normally have a rough hair coat characterized by several rosettes or whorls of hair. Generalized roughness of hair coat is also associated with illness, leaky water bottles, damp and dirty cages, and hypovitaminosis C.

Dermatitis

Bite wounds, usually on the ears, dorsum, or rump, may lead to superficial ulceration of the skin with secondary bacterial contamination. *T. caviae* mite infestation (sarcoptic mange) is



A B

FIGURE 4.8. A: Swelling of the jaw in a guinea pig caused by a tooth root abscess. B: Bacterial cheilitis in a guinea pig. Courtesy of Calgary Avian & Exotic Pet Clinic.

intensely pruritic for most guinea pigs and may be characterized by frantic scratching episodes culminating in seizure-like activity. Other causes of dermatitis include fungal and yeast infections, pediculosis, and cutaneous acariasis. The rabbit ear mite, *P. cuniculi*, may infect guinea pigs when these species are co-housed. Subclinical dermatophyte infection is common and may induce patchy scaling lesions on the face and back. Mites (*Chirodiscoides* spp) tend to affect the trunk, as do bacterial infections, whereas lice are found primarily on the head and neck, and around the nipples (Figure 4.9). Lesions of ectoparasitism are usually exacerbated by scratching, as occurs with *T. caviae* and louse infestation. Preputial dermatitis has been reported in boars and urine scalding is seen in guinea pigs of both sexes housed in wet conditions or with renal disease. Guinea pigs are messy eaters and drinkers, and bedding substrate must be changed regularly to keep the animals clean and dry. Myiasis (fly strike) may occur in guinea pigs housed indoors under unsanitary conditions that permit moist, ulcerative dermatitis to occur. The infestation may go undetected for some time in longer-haired breeds because of hair matting. Pododermatitis may result when guinea pigs are housed on wire flooring (Figure 4.10). A moist dermatitis may result when animals have overgrown cheek teeth with resultant entrapment of the tongue and interference with swallowing ("slobbers"—see below) (Figure 4.11).

Gastrointestinal Conditions

Anorexia

Healthy guinea pigs are generally enthusiastic at mealtime, and anorexia may be a sign of a serious underlying systemic condition (Table 4.7). Overgrowth of molars may result in sharp points on their surfaces that cause discomfort or mucosal laceration during chewing. Guinea pigs may salivate ("slobbers") in cases of malocclusion, particularly if their tongue becomes



FIGURE 4.9. Lice eggs (nits) may be seen deep in the hair coat around the nipple of this young guinea pig.



FIGURE 4.10. Bilateral pododermatitis in a Skinny pig that was housed in a cage with a wire bottom.



FIGURE 4.11. Moist cervical dermatitis or "slobbers" in a guinea pig (left) and chinchilla (right; Courtesy of Calgary Avian & Exotic Pet Clinic) with incisor and cheek teeth malocclusion.

Table 4.7. Common presenting gastrointestinal conditions and differential diagnoses in guinea pigs and chinchillas.[a]

Condition	Differential Diagnoses
Anorexia	Noninfectious
	Dental disease (malocclusion, ptyalism)[a]
	Hypovitaminosis C (scurvy)
	Sudden dietary change
	Pregnancy toxemia
	Insufficient water supply
	Change in husbandry practices (environmental stress)
	Gastric dilatation[a]
	Intestinal accident
	Pain[a]
	Gastric foreign body with peritonitis
	Neoplasia
	Infectious
	Secondary to disease—see below
Diarrhea	Noninfectious
	Dietary indiscretion (carbohydrate overload)
	Low-fiber diet
	Inappropriate use of antibiotics (*C. difficile* overgrowth)
	Intestinal amyloidosis
	Infectious
	Viral enteritis, e.g., coronavirus
	Bacterial enterocolitis, e.g., *C. piliforme* (Tyzzer's disease), *E. coli*, *Salmonella* spp, *Yersinia* spp
	Protozoal infection, e.g., coccidiosis (*E. caviae*), cryptosporidiosis, and giardiasis[a]
Constipation	Noninfectious
	Obesity[a]
	Inappropriate diet[a] (low fiber)
	Lack of exercise[a]
	Colonic atony and fecal impaction (aged boars)

[a]Denotes conditions that may also occur in chinchillas.

entrapped between overgrown molars in the lower dental arcade, when their teeth are sore and loose as occurs with hypovitaminosis C, and following heat stress. Sudden dietary changes, changes in management practices, or insufficient access to clean, fresh water may also induce anorexia, as can pregnancy toxemia. Gastric dilatation with or without volvulus with severe abdominal distension is an acute emergency in guinea pigs, sometimes occurring secondary to rapid dietary changes, and requires immediate deflation by stomach tube or surgical correction to prevent volvulus sequelae (Figure 4.12). The condition is frequently fatal.

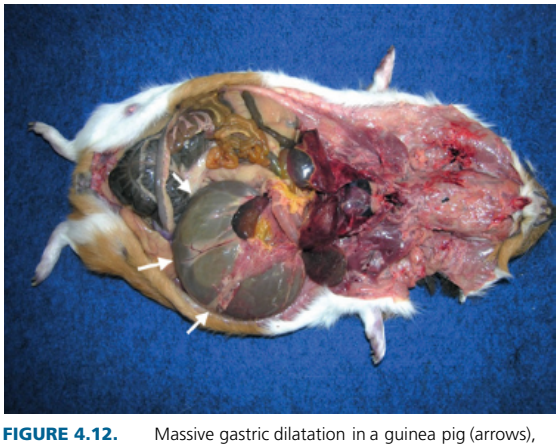


FIGURE 4.12. Massive gastric dilatation in a guinea pig (arrows), diagnosed at necropsy.

Diarrhea

When an enteropathy does occur in a guinea pig, the disease is generally rapidly fatal with few clinical signs. Supportive fluids and supplemental heat can be offered, but the prognosis is generally poor. Infectious causes of diarrhea include Tyzzer's disease

(*C. piliforme* infection), coliform infections, salmonellosis, yersiniosis, a coronaviral wasting syndrome with diarrhea in young pigs, and other clostridial infections, for example, *C. difficile* and *C. perfringens*. Rapidly fatal acute enteritis and typhlitis may result from narrow-spectrum antibiotic administration, which eliminates the normal bacterial flora and induces bacterial overgrowth and dysbiosis. Nematode infections are rare in guinea pigs and are typically subclinical. Cryptosporidiosis, coccidiosis (*E. caviae*), and giardiasis may cause diarrhea, poor weight gain, and, potentially, death in young guinea pigs. Noninfectious causes of diarrhea and ileus are common in guinea pigs and include dietary indiscretion (carbohydrate overload), diets low in fiber, and intestinal amyloidosis secondary to chronic inflammation. Once established, there is no cure for this last condition.

Constipation

Fecal impaction may occur in intact boars, generally greater than 2.5 years of age, secondary to colonic atony, and the condition is treated by regular, gentle manual evacuation of the colon. Following scent marking, intact older males may accumulate shavings, fecal debris, genital secretions, and other material around the anus, forming a dense mat of material known as a scrotal plug, which may make it difficult for them to defecate. Boars should be examined on a regular basis to ensure there is no accumulation of debris around their anus. Obesity, inappropriate diet, and lack of exercise may all contribute to constipation.

Cardiorespiratory Conditions

Heart disease is increasingly recognized in companion guinea pigs and is seen with an incidence of up to ~3% in clinical practice. Congestive heart failure, valvular insufficiency, right-sided heart failure (cor pulmonale), cardiomyopathy (restrictive, hypertrophic and dilated occurring with equal frequency), and idiopathic pericardial effusion have been described. Rhabdomyomatosis, a congenital condition involving storage of glycogen within myofibers, which appears grossly as pale streaking of the heart surface, can be extensive but does not appear to contribute to symptomatic cardiac disease. Similarly, fatty infiltration of the myocardium can be quite extensive but is interpreted as an incidental finding.

Rhinitis, Dyspnea, and Other Respiratory Conditions

Oculonasal discharge frequently accompanies respiratory disease in guinea pigs (Table 4.8). Bacterial organisms that are commonly involved in respiratory disease in guinea pigs

Table 4.8. Common presenting cardiorespiratory conditions and differential diagnoses in guinea pigs and chinchillas.[a]

Condition	Differential Diagnoses
Nasal discharge/ rhinitis/sneezing	Noninfectious
	Dental disease[a] (molar roots)
	Allergy (dust, hay)
	Increased temperature[a]
	Nasal foreign body[a]
	Neoplasia[a]
	Infectious
	B. bronchiseptica[a]
	Other bacterial infections,[a] e.g., *S. aureus, P. multocida, Streptococcus* spp, *Pseudomonas* spp
Dyspnea	Noninfectious
	Stress[a]
	Gastric torsion
	Pregnancy toxemia
	Foreign body
	Aspiration pneumonia
	Neoplasia,[a] e.g., lymphoma with pleural effusion, pulmonary adenoma
	Infectious
	Bacterial pneumonia,[a] e.g., *B. bronchiseptica*, *Streptococcus* spp, *P. multocida, S. aureus, K. pneumoniae*
	Viral infection, e.g., adenovirus, parainfluenza virus, cytomegalovirus

[a] Denotes conditions that may also occur in chinchillas

include *B. bronchiseptica*, *Streptococcus pneumoniae*, and *S. zooepidemicus*. Organisms less frequently involved include *K. pneumoniae, P. multocida, P. aeruginosa*, and *S. aureus*. Systemic infections with parainfluenza virus, adenovirus, and, rarely, cytomegalovirus may result in mild rhinitis and cervical lymphadenopathy. Acute, fatal pneumonia has been reported infrequently following adenoviral infection in young animals. Noninfectious conditions causing respiratory distress are heat stress, sudden fear or excitement with massive catecholamine release, allergy, tooth reserve crown elongation (malocclusion), diaphragmatic hernia, nasal foreign body, pregnancy toxemia, gastric torsion, and some forms of neoplasia, such as lymphoma with pleural effusion.

Endocrine Conditions

Diabetes mellitus has been reported sporadically in guinea pigs. This condition presents as in other animals with polyuria, polydipsia, glycosuria, and ketosis. Moderate-to-marked fatty infiltration of the pancreas occurs frequently with increasing age but is not linked to increased susceptibility to diabetes mellitus. There are rare reports of hyperadrenocorticism (Cushing's disease) in guinea pigs, which have been associated with functional adrenocortical lesions. Successful treatment with trilostane is reported.

Hyperthyroidism is also occasionally seen in aging guinea pigs. A mass may be palpable in the ventral neck, and total T4 serum levels are usually elevated. Most thyroid masses are malignant but medical treatment may significantly increase survival time. Typical signs of thyroid gland tumors are weight loss and increased appetite and activity.

Nervous and Musculoskeletal Conditions

Head Tilt or Torticollis

Head tilt is uncommon in guinea pigs but may be caused by otitis media/interna induced by a bacterial infection (Table 4.9). Encephalopathies that lead to head tilt, such as toxoplasmosis and brain abscesses, are reported rarely. Head tilt has been reported in guinea pigs with insulinoma.

Incoordination and Seizures

A common cause of incoordination or paralysis is nerve, bone, or soft tissue injury from a fall. Guinea pigs have fragile skeletons and must be handled carefully. Pregnancy toxemia, other toxicities, heat stroke, enterotoxemia, streptococcal meningitis, and various muscular disorders (e.g., dystrophies) are other causes of incoordination and, rarely, seizures. Severe sarcoptic mange caused by *T. caviae* may induce intense pruritus, and the constant scratching can lead to fits of muscle spasms or spontaneous epileptic seizures caused by generalized pruritus-induced hyperesthesia. Rabies virus infection is highly uncommon in guinea pigs in North America but has been reported in guinea pigs with outdoor access.

Paresis or Paralysis

Hypovitaminosis C, characterized by subperiosteal hemorrhage and swollen and painful joints, is a common cause of immobility in guinea pigs. Affected animals may squeal when restrained and have concurrent poor hair coats, anorexia, and tooth mobility. Poor wound healing and conjunctival or intraocular bleeding may also be observed. Systemic diseases, such as *B. bronchiseptica* infection, streptococcosis with secondary polyserositis, and salmonellosis, also may result in reluctance to move. Osteoarthritis, severe pododermatitis with secondary osteomyelitis, spinal fracture, and various diet-related myopathies are other possible causes of paresis and paralysis. Back injury with edema and hemorrhage around the spinal cord may result in temporary paralysis. Osteodystrophy fibrosa or nutritional secondary hyperparathyroidism has been reported in guinea pigs fed diets high in calcium, for example, alfalfa-based diets. Guinea pigs, especially if housed in large round or square cages, may run in circles when excited. Stampeding guinea pigs, circling or not, may leap from an open-topped cage regardless of the height above the floor, resulting in trauma and fractures. Rectangular cages and cage furniture or barriers within the cage discourage this type of circling.

Ocular Conditions

Conjunctivitis in guinea pigs is commonly due to a bacterial infection in a marginally scorbutic animal. Animals present with swollen lids with a moderate serous, mucopurulent discharge or flaky crusting. Bacteria involved may include *B. bronchiseptica, Streptococcus* spp, *S. aureus*, or *Pasteurella* spp. *Chlamydia caviae* infection causes inclusion body conjunctivitis in young animals. This infection is generally self-limiting, lasting about 3 weeks, but may also recur on a cyclical basis in some animals. Chlamydiosis presents as mild chemosis and conjunctivitis with a serous or mucopurulent discharge. Panophthalmitis may be caused by the bacteria noted, including *S. zooepidemicus*.

Cataracts are seen as an autosomal dominant condition in some guinea pig strains and may be associated with diabetes mellitus or with a deficiency of L-tryptophan. Long-term open lids, as may occur during anesthesia, can lead to corneal, anterior chamber, and lens dessication. Sterile ophthalmic lubricant should always be used, in addition to oxygen supplementation by face mask or nasal tube, if injectable anesthetics are used, and tarsorrhaphy may be considered for longer procedures.

"Pea eye" involves the unilateral or bilateral formation of hyperplastic nodules of the lacrimal or zygomatic glands, which may be located on the inferior conjunctival surface. Removal of the nodules is not advised unless the masses are so large as to cause exposure keratitis.

Other ocular conditions reported in guinea pigs include osseous choristoma (ectopic mineralization of the ciliary body), lymphosarcoma with conjunctival involvement, and conjunctival dermoid.

Table 4.9. Common presenting nervous and musculoskeletal conditions and differential diagnoses in guinea pigs and chinchillas.[a]

Condition	Differential Diagnoses
Head tilt/torticollis	Noninfectious
	Trauma[a]
	Toxoplasmosis
	Cerebrovascular accident
	Toxins, e.g., lead (paint)
	Infectious
	Otitis media/interna secondary to bacterial infection,[a] e.g., *B. bronchiseptica*, *Streptococcus* spp, other Gram-negative bacteria
	Brain abscess[a]
Seizures	Noninfectious
	Pregnancy toxemia
	Heat stroke[a]
	Toxins, e.g., lead (paint)
	Hypoxia[a]
	Severe systemic disease[a]
	Severe sarcoptic mange infestation
	Neoplasia[a]
	Trauma[a]
	Infectious
	Bacterial encephalitis/meningitis/abscess,[a] e.g., *Streptococcus pneumoniae*, *P. multocida, S. aureus*
	Rabies virus
	Sarcoptic mite infestation
Paresis/paralysis	Noninfectious
	Trauma[a] (leg/muscle)
	Heavily pregnant sows
	Hypovitaminosis C (swollen joints, fractures, periarticular hemorrhage)
	Dietary deficiencies,[a] e.g., hypovitaminosis E
	Pododermatitis with osteomyelitis
	Osteoarthritis
	Severe inanition[a]
	Toxicity, e.g., lead (paint)
	Infectious
	Polyserositis/arthritis,[a] e.g., streptococcal infection
	Spinal abscess[a]
	Toxoplasmosis
	Rabies virus

[a] Denotes conditions that may also occur in chinchillas.

Genitourinary Conditions

Renal Conditions

Urolithiasis is common in both male and female guinea pigs (Table 4.10). Normal guinea pig urine is thick, pale yellow, and cloudy. Calculi can occur at any site along the urinary tract and are usually composed of calcium carbonate salts. Ureteral calculi are virtually impossible to remove due to the small diameter of the guinea pig ureters. Urethral calculi in males may sometimes be retropulsed into the bladder prior to cystotomy; in females, they may pass spontaneously. In males, manual removal of a distal urethral calculus by everting the most distal aspect of the urethra is sometimes possible. In females, placement of hooks of a self-retaining ring retractor around the urethra to enlarge the opening allows visibility of most urethral calculi and their removal. Bacterial cystitis occurs more commonly in older sows and may be caused by *Streptococcus* spp., *S. aureus*, *E. coli, or Corynebacterium* spp. infection.

Table 4.10. Common presenting genitourinary conditions and differential diagnoses in guinea pigs and chinchillas.[a]

Condition	Differential Diagnoses
Renal conditions	Noninfectious
	Urolithiasis
	Chronic renal failure[a]
	Hypervitaminosis D (dystrophic mineralization)
	Fatty infiltration due to pregnancy toxemia
	Hydronephrosis[a]
	Toxicoses, e.g., gentamycin, NSAIDs
	Renal cysts
	Neoplasia,[a] e.g., lymphoma
	Infectious
	Pyelonephritis/nephritis/cystitis secondary to bacterial infection,[a] e.g., *Streptococcus* spp, *S. aureus, E. coli, Yersinia* spp
	Renal abscess[a]
Uterine/ovarian conditions	Coccidiosis, e.g., *Klossiella cobayae*
	Noninfectious
	Cystic endometrial hyperplasia[a]
	Cystic rete ovarii
	Dystocia, e.g., oversized pups, inability of pubic symphysis to separate, uterine torsion, obesity, uterine inertia
	Pregnancy toxemia
	Infertility,[a] e.g., inadequate protein, hypovitaminosis A, D, E, or hypervitaminosis A, behavioral problems
	Abortion,[a] e.g., stress, hyperthermia, trauma, bacterial or viral infection
	Neoplasia,[a] e.g., uterine leiomyoma[a]
	Infectious
	Pyometra/metritis following bacterial infection,[a] e.g., *B. bronchiseptica, Streptococcus* spp, *E. coli, S. aureus*
Mammary gland conditions	Noninfectious
	Mammary gland hyperplasia/dysplasia
	Agalactia[a]
	Neoplasia[a]
	Infectious
	Mastitis,[a] e.g., *S. aureus, Klebsiella* spp, *E. coli, Pasteurella* spp
Male reproductive conditions	Noninfectious
	Intestinal herniation and strangulation postcastration
	Scrotal plugs
	Trauma
	Neoplasia
	Infectious
	Orchitis and epididymitis[a] following *B. bronchiseptica* and *Streptococcus* spp infection

[a] Denotes conditions that may also occur in chinchillas.

Chronic renal failure is common in older guinea pigs of both sexes. The disease is likely multifactorial and may involve inappropriate diets, fatty infiltration of the kidney following pregnancy toxemia, dystrophic mineralization following inappropriate vitamin D supplementation or other toxicities, autoimmune disease, infectious agents, chronic antigenic stimulation, and vascular disease. Renal cysts and neoplasia are uncommon.

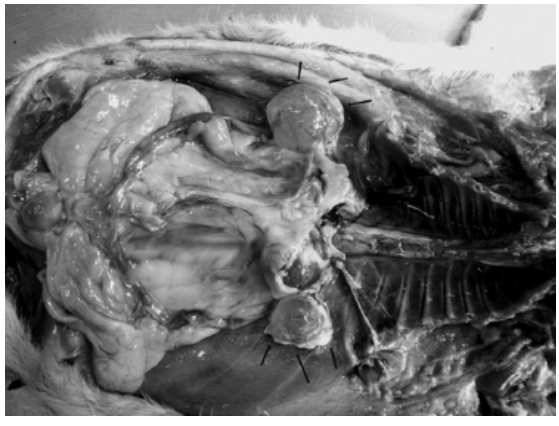


FIGURE 4.13. Bilateral cystic rete ovarii (arrows) in an aged sow.



FIGURE 4.14. Prolapsed vagina in a guinea pig.

Infertility

Real or apparent infertility or decreased litter size in guinea pigs may be related to age at the time of breeding, stress from management changes, estrogens in the feed, bedding or other debris adhering to the genitalia (scrotal plugs), increased ambient temperature, nutritional deficiency, metritis, environmental stress, conspecific aggression or incompatibility, or discomfort secondary to preputial dermatitis.

Prenatal Mortality

Dystocia is common in sows because of the large size of the precocious offspring. Sows bred after mineralization of the fibrocartilaginous joint that forms the pubic symphysis often have difficulty birthing. Uterine torsion, obesity, and uterine inertia may all contribute to dystocia. Abortions and stillbirths in guinea pigs occur with nutritional deficiencies, bacterial metritis or orchitis, viral infection (e.g., guinea pig cytomegalovirus), stress, hyperthermia, trauma, and pregnancy toxemia.

Litter Desertion or Death

Neonatal guinea pigs are precocious, and maternal attention, other than nursing and grooming, is not necessary for survival. However, the mother should remain with the young, if at all possible, for at least the first 2 weeks following birth. Factors that reduce maternal attention include mastitis, maternal inexperience, and environmental disturbances, such as noise or active cagemates. Young that weigh less than 60 g at birth usually die within a few days.

Other Conditions

Ovarian cysts are common in sows and are mainly nonfunctional serous cysts (rete ovarii cysts) or, less commonly, follicular. Cystic rete ovarii occur commonly in aged sows (Figure 4.13). Uterine leiomyoma is frequently seen in conjunction with these cysts. Mammary gland tumors occur with equal frequency in boars as in sows. As in rabbits, the inguinal canal remains open in boars throughout life, and intestinal herniation and strangulation may occur if the rings are not closed at neutering. Uterine prolapse may occur rarely (Figure 4.14).

Sudden Death

Death with few or no preceding signs may be caused by sudden stress or fear, chilling of pups or overheating animals of any age, septicemia or toxemia (salmonellosis, typhlitis, enteritis, pregnancy toxemia, antibiotic toxicity), pneumonia, gastric volvulus, dystocia, or dehydration.

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THE CHINCHILLA

Chinchillas and guinea pigs are similar species in many respects and share propensities for developing certain diseases. Conditions seen in both guinea pigs and chinchillas have been indicated in the preceding tables for guinea pigs, and the text comments for these conditions apply to chinchillas equally. This section will only cover conditions specific to chinchillas.

Skin Conditions

The dense hair coat of chinchillas is usually not permissive to ectoparasite infestation; however, dermatophytosis is quite common, either as clinical or subclinical disease, and subcutaneous abscesses may also occur. Fur chewing may be seen as a behavioral vice and may be related to stress. Hair is typically chewed over the dorsum but is of normal length over the head and tail tip. Intercurrent disease should be ruled out and cases may be managed through changes in husbandry, environmental conditions, resources provided, etc. Seborrhea and matted hair coats may result if chinchillas are not given regular access to a dust bath. Fur slip is a condition unique to chinchillas and presents as clumps of hair that fall out or are left in one's hand when chinchillas are stressed and simultaneously grasped superficially, for example, during a clinical examination. This is an escape mechanism, allowing the animal to avoid the perceived threat. Depending on the stage of the hair cycle that follicles are in when fur slip occurs, it may be months before the coat regrows completely. Chinchillas should not be scruffed for restraint, for this reason, but should be firmly held around the body. Dermatophytes are common causes of alopecia in chinchilla.

Streptococcus equi subspecies *zooepidemicus* has been isolated from a number of chinchillas with subcutaneous abscesses in the past decade, and it is considered an emerging pathogen for this species.

Gastrointestinal Conditions

Malocclusion from molar crown elongation occurs in chinchillas and may result in anorexia if animals are unable to close their mouth or chew. Ptyalism may also be an indication of dental disease in chinchillas, and animals may not show clinical signs until the disease is advanced, resulting in a poor prognosis. Cavities, tooth resorption, and periodontal disease are also common in chinchilla.

Gastric stasis, ileus, and enteritis are also seen frequently in chinchillas from similar conditions to those reported for guinea pigs. Dense mats of ingested hair may rarely lead to gastric obstruction.

Cardiorespiratory Conditions

Because of their dense fur coats and inability to sweat, chinchillas are particularly susceptible to heat stroke and sudden collapse with rapid death. Cardiomyopathy has been reported

rarely in chinchillas. Bacterial pneumonias occur with equal frequency in chinchillas and are usually of Gram-negative origin, for example, *Bordetella* spp., *Klebsiella* spp., *Pasteurella* spp., and so forth. Cardiac murmurs are common in chinchillas, and a significant number are heard in the absence of cardiac valvular disease (i.e., physiologic murmurs).

As more companion chinchillas are imaged, more cases of otitis media are identified and *P. aeruginosa* is commonly isolated. Inflammatory polyps have also been encountered in the middle ear, as seen in dogs and cats

Endocrine Conditions

Endocrine disease is uncommon in chinchillas. Diabetes mellitus has been reported sporadically.

Nervous and Musculoskeletal Conditions

Chinchillas are able to formulate adequate amounts of vitamin C from their diet and do not develop scurvy, as do guinea pigs. They are a more athletic, faster-moving animal than guinea pigs and tend not to experience as many traumatic injuries after falls, except for tibial fractures. Because of their very large tympanic bullae, head tilt following bacterial otitis media/interna infection may be seen in chinchillas, and the infectious agents are the same as for guinea pigs. *P. aeruginosa* may also cause otitis interna in chinchillas. Pododermatitis is not a significant disease entity in chinchillas. Chinchillas are very susceptible to encephalitis following listeriosis. This condition may also result in enteritis and diarrhea and is often rapidly fatal. Fatal cerebrospinal nematodiasis caused by *Baylisascaris procyonis* larvae can occur if chinchilla feed or bedding becomes contaminated with raccoon feces. Idiopathic epilepsy has also been observed. Because of their long hind limbs, chinchillas are relatively prone to tibial fractures.

Ocular Conditions

Asteroid hyalosis and cataracts may be seen in older animals. Exophthalmos caused by orbital *Taenia* coenurus or retrobulbar abscess is reported in the chinchilla. Conjunctivitis is not uncommon in chinchillas, affecting up to 8% of animals seen in one study, and may be associated with irritation from excessive sand bathing, poor environmental ventilation, nasolacrimal duct obstruction or Gram-negative bacterial infections (e.g., *P. aeruginosa*, often with simultaneous upper respiratory signs). Epiphora or "wet eye" has been associated with dental disease due to compression of the nasolacrimal duct.

Genitourinary Conditions

Urolithiasis can occur in chinchillas, most commonly calcium carbonate, and it is more often seen in males. Semen-matrix calculi have also been described. Like guinea pigs, chinchilla young are fully developed at birth (precocious); however, the pups tend to be smaller at birth and dystocia is uncommon in chinchillas. Fur ring with secondary paraphimosis or balanoposthitis occurs in boars. The circumferential ring of hair can be lubricated and slipped off the end of the penis to reduce the constriction. Penile prolapses may also occur, although the etiology is unknown. The penis should be kept clean and lubricated, and the prognosis is generally good for spontaneous resolution. The chinchilla does not have a true scrotum; rather, they have pouches that support the caudal epididymis. This normal anatomical arrangement should not be mistaken for cryptorchidism.

Sudden Death

Sudden death without clinical signs in chinchillas is caused most commonly by heat stroke, peracute systemic disease, for example, pneumonia or listeriosis, sudden stress or fright, cardiac disease, or enterotoxemia.

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THE HAMSTER

Skin Conditions

Alopecia

Low-protein diets (less than 16% crude protein) may contribute to alopecia in hamsters, and nutritional information should be reviewed carefully when purchasing food (Table 4.11). Aged, immunologically compromised hamsters may develop demodicosis with alopecia, scaliness, and pustules over the rump and back. Less commonly, hamsters may also develop dermatophytosis, hereditary hairlessness, hair loss associated with an endocrine neoplasm or chronic renal disease, epitheliotropic lymphoma (Figure 4.15), or mechanical loss from constant rubbing on a cage or feeder. Male hamsters housed together may cannibalize the flank glands of one another. Loss of facial hair occurs occasionally around the vibrissae, likely due to mechanical abrasion.

Swellings and Masses

Normal structures in hamsters often thought erroneously to be abnormal swellings are the pendulous testes, distended cheek pouches, and the paired flank glands. Note that the flank glands are found on the sides of Syrian hamsters but are on the ventrum of dwarf hamsters, similar to the gerbil ventral marking gland. Pathologic processes causing palpable swellings include abscesses, various neoplasms such as flank gland tumors (Figure 4.16), melanoma, lymphoma, and mastocytoma, mastitis, impacted cheek pouches, and, rarely, granulomas in the skin and lymph nodes caused by *Mycobacterium* spp. Fighting, with secondary abscesses, is common, and females tend to be more aggressive than males. Impacted cheek pouches are readily treated by everting them under anesthesia and gently cleaning out the inspissated material. Cutaneous epitheliomas and transmissible lymphomas are thought to be due to hamster polyomavirus infection.

Rough Hair Coat

Hamsters in cages with leaking water bottles and soiled bedding; with polyuria, endocrine dysfunction, or diarrhea; and those housed with incompatible cagemates may have rough hair coats. A rough hair coat is a nonspecific sign of fighting, inadequate diet or management, aging, or disease.

Dermatitis

Inflammation of the skin is most often seen in association with bite wounds and secondary infection with bacteria such as *S. aureus, Rodentibacter* complex (previously *Pasteurella pneumotropica*), or *Streptococcus* spp. Other possible causes of dermatitis include demodectic mange; *Notoedres* spp. infection, which produces crusty lesions around the ear, nose, feet, and perianal area; and dermatophytosis. Demodectic mange may also induce a greasy, matted coat and occurs most often in immunocompromised older animals with concurrent disease. Abrasion of the skin by wood shavings has also been reported.

Gastrointestinal Conditions

Anorexia

As for other rodents, the incisors of hamsters continue to grow throughout life. If malocclusion results, animals may not be able to prehend food properly, and anorexia with or without excessive salivation may result (Table 4.12). Dental deformities and domed calvaria have been reported in young hamsters

Table 4.11. Common presenting skin conditions and differential diagnoses in hamsters.

Condition	Differential Diagnoses
Alopecia	Noninfectious Fighting/trauma Hereditary hairlessness Mechanical, e.g., feeder Nutritional deficiencies, e.g., zinc, protein Endocrine-associated, e.g., Cushing's disease Contact allergy Neoplasia, e.g., lymphoma Infectious Dermatophytosis, e.g., *Trichophyton* spp Demodicosis, e.g., *D. aurati, D. criceti*
Swellings/masses	Noninfectious Trauma/hemorrhage Impacted cheek pouches Neoplasia (flank gland tumors, mammary, melanoma, basal cell tumors, fibrosarcoma, lymphoma, mammary adenocarcinoma) Infectious Abscesses, e.g., *Staphylococcus* spp, *Proteus* spp Granulomas Mastitis
Dermatitis	Noninfectious Fighting/bite wounds Nutritional deficiencies, e.g., low protein Wet or abrasive bedding Endocrinopathy (e.g., hyperadrenocorticism) Infectious Bacterial, e.g., *Staphylococcus* spp Dermatophytosis, e.g., *Trichophyton* spp Parasitic, e.g., mites (*Notoedres* spp, *Demodex* spp)



FIGURE 4.15. Cutaneous lymphosarcoma in a hamster. The condition causes irregular thickening, crusting and ulceration of the skin.



FIGURE 4.16. Flank gland tumor in a male hamster.

Table 4.12. Common presenting gastrointestinal conditions and differential diagnoses in hamsters.

Condition	Differential Diagnoses
Anorexia	Noninfectious
	Dental disease (malocclusion, deformities)
	Insufficient water supply
	Intestinal accident
	Amyloidosis
	Pain
	Neoplasia
	Infectious
	Secondary to disease—see below
Diarrhea	Noninfectious
	Dietary indiscretion (carbohydrate overload)
	Low-fiber diet
	Inappropriate use of antibiotics (*C. difficile* overgrowth)
	Intestinal amyloidosis
	Infectious
	Bacterial enterocolitis, e.g., *Lawsonia intracellularis*, *C. piliforme* (Tyzzer's disease), *C. perfringens*, *C. difficile*, *E. coli*, *Salmonella* spp
	Protozoal infection, e.g., giardiasis, spironucleosis
Constipation	Noninfectious
	Obesity
	Inappropriate diet (low fiber)
	Lack of exercise
	Infectious
	Cestode impaction, e.g., *Rodentolepis* spp, *Hymenolepis* spp

following infection of the dam while pregnant with hamster parvovirus. Other causes of anorexia or inappetence include systemic disease, lack of access to clean potable water, intestinal accidents such as intussusception with heavy cestode burden, pain from any source, or neoplasia. Multicentric lymphoma is commonly seen as hamsters age and may induce inappetence and weight loss.

Diarrhea

The vague term "wet tail" is the everyday synonym for the diarrheal complex that may occur in hamsters. Proliferative enteritis is common in young animals and is caused by *L. intracellularis* infection, which confers a thickened, corrugated appearance to the intestinal serosa. Diarrhea in hamsters may also result from coliform and clostridial infection, salmonellosis, Tyzzer's disease (*C. piliforme* infection), intestinal or hepatic amyloidosis, protozoal overgrowth of *Giardia* spp. or *Spironucleus* spp., or cecal dysbiosis following narrow-spectrum antibiotic administration with development of secondary clostridial enterotoxemia. Treatment of *Salmonella* spp. infections in any small mammal pet is controversial because the condition is zoonotic, and treatment may lead to a carrier state with bacterial shedding into the environment.



FIGURE 4.17. Prolapsed rectum in a hamster at post mortem.

Sequelae to diarrhea may include intestinal obstructions, intussusception, or rectal prolapse (a dark red tubular protrusion from the anus) (Figure 4.17). Reduction of the prolapsed rectum is frequently unsuccessful unless the underlying etiology is resolved.

Constipation

Constipation in hamsters may be related to *Rodentolepis nana* and *Hymenolepis diminuta* cestode infestations in the small intestine as well as obesity, lack of adequate fiber in the diet, lack of exercise, or bedding ingestion with subsequent impaction. In general, cestode infestation is innocuous and subclinical in hamsters. Both *R. nana* and *H. diminuta* are zoonotic, and *R. nana* may be transmitted directly to humans without an intermediate host.

Oxyuriasis is common, usually involving species that affect other rodents (i.e., *Syphacia* spp); however, heavy burdens may be maintained with no apparent clinical signs.

Cardiorespiratory Conditions

Nasal Discharge

Nasal discharge is uncommon in hamsters but may be induced by irritation from volatile oils found in softwood bedding that has not been kiln dried (Table 4.13). Purulent nasal discharge may be seen with bacterial pneumonia. Neoplasms other than nasal polyps are rare in hamsters, as is bacterial rhinitis.

Dyspnea

Both cardiomyopathy and atrial thrombosis are common in aging hamsters. Typical signs of disease include cyanosis, weight loss, reduced activity, and rapid, shallow breathing. Cardiomyopathy is a progressive, autosomal recessive condition in some strains of Syrian hamsters. Treatment of cardiomyopathy is symptomatic, and drug doses may be extrapolated from other small animal species, with careful monitoring. Left atrial thrombosis occurs more commonly in female hamsters and at an earlier age than in males. The disease appears to be related to androgen levels, as neutered males have an increased susceptibility to developing the disease compared with intact males.

Respiratory disease is also common in hamsters, and most frequently induced by bacterial infections, such as *Streptococcus* spp., *Rodentibacter* complex, *Bordetella* spp., or *K. pneumoniae*. Viral rhinitis and pneumonia secondary to Sendai virus infection tend to be subclinical and mild but may predispose animals to more serious secondary bacterial infections. Heat stress, severe systemic disease of any cause, aspiration of bedding or food, and neoplasia may also induce dyspnea in hamsters.

Endocrine Conditions

Adrenocortical disease is one of the most common conditions of hamsters, frequently affecting older males, and may result from either primary hyperadrenocorticism (adrenocortical hyperplasia or adenoma) or secondary hyperadrenocorticism following ACTH release from a pituitary tumor. The clinical signs are typical, including bilaterally symmetrical flank alopecia, hyperpigmentation, comedones, polyuria, and polydipsia. Hamsters secrete both cortisol and corticosterone, so serum cortisol results may not be diagnostic. The diagnosis is often based on clinical signs, and defining an appropriate medical treatment regime is difficult.

Diabetes mellitus can be seen in hamsters and presents as weight loss, polyuria, polydipsia, and glycosuria. Treatment is supportive with weight management, reduction of carbohydrate-rich treats, and insulin.

Both thyroid gland tumors (carcinoma) and hypothyroidism are reported in Syrian hamsters.

Table 4.13. Common presenting cardiorespiratory conditions and differential diagnoses in hamsters.

Condition	Differential Diagnoses
Nasal discharge/rhinitis/ sneezing	Noninfectious Irritation (volatile oils from softwood bedding), nasal polyps Infectious Bacterial infection, e.g., *Rodentibacter* complex, *S. aureus, Streptococcus* spp
Dyspnea	Noninfectious Heat stress Primary cardiac disease (cardiomyopathy, atrial thrombosis) Systemic disease Aspiration pneumonia Neoplasia, e.g., lymphoma with pleural effusion, pulmonary adenoma Infectious Bacterial pneumonia, e.g., *B. bronchiseptica*, *Streptococcus* spp, *Rodentibacter* complex, *S. aureus, K. pneumoniae* Viral infection, e.g., Sendai virus

Nervous and Musculoskeletal Conditions

Trauma and musculoskeletal injury are common in hamsters, due to fighting, entrapment of a limb in mesh sides or bottom of the cage or running wheel, falls, and excessive restraint (Table 4.14). Hamsters are an important zoonotic source of lymphocytic choriomeningitis virus (LCMV) infection. The condition is generally subclinical in hamsters but may be transmitted to human handlers during routine handling who are at risk of developing neurological disease. Appropriate hand washing should always be undertaken after handling hamsters. Other nervous and musculoskeletal conditions in hamsters are rare.

Ocular Conditions

Bacteria, bedding dust, bite wounds, and LCMV infection can cause conjunctival reaction or infection in hamsters. A hamster-specific cytomegalovirus has been reported to induce sialodacryoadenitis in Chinese hamsters. Tooth root infections can extend into the orbit forming a retrobulbar abscess, and trauma to the eyeball may lead to corneal opacity or rupture of the globe. Exophthalmos may occur with ocular infection, periorbital trauma, or obesity. Iatrogenic proptosis may be induced in hamsters during restraint because of their shallow orbits. The eye can be enucleated or sometimes can be carefully cleaned and replaced, using sterile lubricant, under anesthesia.

Genitourinary Conditions

Renal Conditions

Chronic renal failure is common in aging hamsters and is often caused by an idiopathic condition (nephrosclerosis) or renal amyloidosis (Table 4.15). Clinical signs include weight loss, anorexia, ascites, polyuria, and polydipsia. Treatment is supportive and the prognosis is poor. Multiple renal, hepatic, or biliary cysts are occasionally noted at necropsy in older Syrian hamsters. Cysts are thin-walled and filled with clear fluid. They are likely congenital in nature and are considered incidental.

Table 4.14. Common presenting nervous and musculoskeletal conditions and differential diagnoses in hamsters.

Condition	Differential Diagnoses
Head tilt/torticollis	Noninfectious Trauma Cerebrovascular accident Toxins, e.g., lead (paint) Neoplasia Infectious Otitis media/interna secondary to bacterial infection, e.g., *Rodentibacter* complex, *S. aureus* Brain abscess
Seizures	Noninfectious Heat stroke Hypoxia Idiopathic seizure Severe systemic disease Neoplasia Infectious Bacterial encephalitis/meningitis/abscess, e.g., *Streptococcus* spp
Paresis/paralysis	Noninfectious Trauma (leg/muscle) Compression (excessive restraint) Fractures, e.g., osteoporosis Osteoarthritis Severe anemia, e.g., tumor Severe inanition Infectious Spinal abscess

Table 4.15. Common presenting genitourinary conditions and differential diagnoses in hamsters.

Condition	Differential Diagnoses
Renal conditions	Noninfectious
	Chronic renal failure (nephrosclerosis)
	Hydronephrosis
	Amyloidosis
	Polycystic disease
	Neoplasia, e.g., lymphoma
	Infectious
	Pyelonephritis/nephritis/cystitis secondary to bacterial infection, e.g., *S. aureus, E. coli*
	Renal abscess
Uterine/ovarian conditions	Noninfectious
	Cystic endometrial hyperplasia
	Infertility, e.g., inadequate protein or fat, inappropriate light cycle, senescence, immaturity, mate incompatibility, low ambient temperature
	Abortion, e.g., stress, hyperthermia, trauma
	Neoplasia, e.g., granulosa cell tumor, uterine adenocarcinoma
	Infectious
	Pyometra/metritis following bacterial infection, e.g., *P. multocida, S. aureus*
Mammary gland conditions	Noninfectious
	Neoplasia
	Infectious
	Mastitis, e.g., *S. aureus*
Male reproductive conditions	Noninfectious
	Trauma
	Neoplasia
	Infectious
	Orchitis and epididymitis following fighting injury and bacterial infection

Reproductive Conditions

Female hamsters normally produce a copious stringy discharge post ovulation, which has a distinctive smell. This should not be mistaken for pyometra, which is rare in hamsters. Ovarian thecal or granulosa cell tumors occur with relatively high frequency, and uterine adenocarcinoma is common in certain lines of dwarf hamsters. Mammary conditions including mastitis and mammary adenocarcinoma are seen sporadically in hamsters. Treatment for most reproductive conditions is ovariohysterectomy.

Infertility

Actual or apparent infertility in hamsters may be due to immaturity (younger than 5 weeks) or senescence (older than 15 months), low-protein or low-fat diets, cold ambient temperatures, prolonged darkness with or without single, short light exposures every 24 hours (reversible), normal winter breeding quiescence, pair incompatibility, inadequate nest, or using anestrus females just removed from an all-female group. Infertility in young female hamsters may occur if excessive hair surrounding the vulva prevents penile penetration during copulation attempts. Virgin hamsters older than 6–7 months exhibit a high degree of infertility on first breeding.

Prenatal Mortality

Nutritional deficiencies (caloric or protein), systemic disease, large fetal loads, and environmental stress may lead to fetal loss. Maternal destruction of neonates or sucklings, usually accompanied by cannibalism, is common among hamsters, especially in group-housed hamsters with a strong sense of territory. Cannibalism can be precipitated by handling the young (when younger than 10 days) or the nest, disturbing the mother, leaving the male in the cage beyond 1 week postpartum, not providing adequate enclosure space, nesting material or privacy, agalactia or mastitis, noise, changing the husbandry routine, the presence of sick or deformed young, or insufficient feed or water. There is little difference in maternal behaviors between primiparous and multiparous dams.

Sudden Death

Death after nonspecific signs or without preceding signs may be due to such geriatric conditions as atrial thrombosis, amyloidosis (more common in females), cardiomyopathy, renal disease, and neoplasia. Other fatal conditions include trauma, inadequate access to water, enteric disease, chilling or overheating, and antibiotic-induced intestinal dysbiosis. Rare conditions resulting in sudden death include salmonellosis, tularemia, streptococcal infection, and pregnancy ketosis. Hamsters may estivate if the ambient temperature drops below 15 °C and may appear comatose or dead. This should not be mistaken for sudden death and animals may be revived with judicious rewarming.

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THE GERBIL

Skin Conditions

Alopecia

Mechanical irritation with a resulting bald nose may occur if there are rough points on the feeder or cage and barbering will occur if animals are overcrowded (Table 4.16). Endocrine-associated bilaterally symmetrical alopecia is relatively common in older gerbils and often is secondary to cystic ovaries or hyperadrenocorticism. Fighting, trauma, poor diets, and high relative humidity are also associated with hair loss. Degloving injuries of the tail (tail slip) may occur when the tip is grasped. This is treated with amputation proximal to the injury.

Swellings and Masses

Tail and perianal abscesses may occur from fighting if animals are overcrowded. Spontaneous neoplasms occur in gerbils typically over 2 years of age, with the highest incidences in the skin, reproductive tract, and adrenal glands. Neoplasms have also been reported in the thyroid, thymus, liver, kidney, pancreas, and bone. The most common tumor is associated with the ventral marking gland and may be a benign sebaceous adenoma or malignant squamous cell carcinoma or adenocarcinoma (see Figure 3.58). Complete resection can be curative, but ventral marking gland tumors may invade locally and metastasize to lymph nodes and lung. The most common cutaneous tumors in gerbils are melanomas and squamous cell carcinomas. Other tumors include mastocytoma, epitheliotropic lymphoma, basal cell carcinoma, and aural cholesteatoma. This last tumor, despite its name, is not a true neoplasm; it comprised concentric accumulations of keratinized epithelium, and is only found in gerbils and humans. Spontaneous mammary tumors have not been reported in gerbils.

Dermatitis

Ectoparasite infestations are uncommon but can be treated with amitraz or ivermectin when they occur. Focal ulcerative dermatitis may be seen with *Demodex meroni* infestation and fur mites (*Acarus farris* and *Liponyssoides sanguineus*). Nasal dermatitis ("sore nose") is common, with or without conjunctivitis and forepaw dermatitis, particularly in group-housed animals stressed by overcrowding, dirty bedding, and high intracage humidity (Figure 4.18). Sore nose is thought to be due to hypersecretion of porphyrins by the Harderian gland, which accumulates around the nares and eyes and irritates the skin. The condition can lead to self-trauma and frequently focal ulceration with secondary staphylococcal infection. Improving general management and husbandry, reducing overcrowding, and providing gerbils with a sand bath at regular intervals may all assist with clearing this condition.

Table 4.16. Common presenting skin conditions and differential diagnoses in gerbils.

Condition	Differential Diagnoses
Alopecia	Noninfectious Fighting/trauma Mechanical, e.g., food hopper Nutritional deficiencies, e.g., protein High relative humidity (>50%) Endocrine-associated, e.g., Cushing's disease, ovarian cysts Infectious Dermatophytosis, e.g., *Trichophyton* spp Demodicosis, e.g., *D. aurati, D. criceti*
Swellings/masses	Noninfectious Trauma/hemorrhage Neoplasia, e.g., ventral marking gland tumor, melanoma, aural cholesteatoma, basal cell carcinoma, squamous cell carcinoma, epitheliotropic lymphoma Infectious Abscesses, e.g., *Staphylococcus* spp, *Proteus* spp Mastitis
Dermatitis	Noninfectious Fighting/bite wounds Nutritional deficiencies, e.g., low protein Tail slip Coarse bedding Lack of dust bath (nasal dermatitis) Infectious Bacterial, e.g., *Staphylococcus* spp Infection of the ventral marking gland Dermatophytosis, e.g., *Trichophyton* spp Parasitic, e.g., mites (*Acarus* spp, *Demodex* spp)



FIGURE 4.18. Nasal dermatitis in a gerbil.

Gastrointestinal Conditions

Major gastrointestinal conditions of gerbils are very similar to those seen in hamsters (refer to Table 4.12). Gerbils are exquisitely sensitive to *C. piliforme* infection and will often be found dead peracutely following infection. *Citrobacter rodentium* has also been associated with massive outbreaks of diarrhea and mortality in colonies of gerbils. Gerbils may occasionally be infested with an intestinal pinworm, *Dentostomella translucida*, or other species of rodent pinworms (*Syphacia* spp); however, these infestations tend to be subclinical, even with relatively heavy burdens. Obesity and hypercholesterolemia are common in gerbils fed all seed diets, particularly sunflower seeds. Owners should be advised to purchase an appropriate high-quality pelleted diet and to only feed seeds as an occasional treat.

Cardiorespiratory Conditions

Myocardial degeneration may occur spontaneously in gerbils and Tyzzer's disease can result in focal nonsuppurative myocarditis. A serous nasal discharge may be associated with heat stress, allergy, or, rarely, respiratory infection. Pneumonia is seen infrequently in pet or laboratory gerbils and tends to be due to Gram-negative bacterial infection. Pulmonary edema or pleural effusion from mediastinal masses or diaphragmatic hernia also may cause dyspnea.

Endocrine Conditions

Diabetes mellitus has been reported as a sequela to obesity in gerbils. Clinical signs are typical of those seen in other small animal species and include polydipsia, polyuria, glycosuria, and hyperglycemia. Dietary management with weight loss has been described for treatment. Hyperadrenocorticism secondary to adrenal gland or pituitary tumors is rarely reported in gerbils and may be associated with symmetrical alopecia, polydipsia, and polyuria. Cystic ovaries occur commonly in older females and can induce abdominal distension, dyspnea, and endocrine-associated alopecia. Ovariohysterectomy is curative.

Nervous and Musculoskeletal Conditions

Gerbils routinely stomp their feet rapidly to communicate or signal danger to other gerbils. This should not be misinterpreted as seizure activity or ataxia.

Head Tilt

Otitis interna or encephalitis may cause a head tilt, although gerbils have a seeming resistance to otitis media. Such resistance may be associated with an effective ear drainage system. Keratin plugs produced by aural cholesteatomas may also induce head tilt.

Incoordination and Seizures

Epileptiform seizures in gerbils are hypnotic, cataleptic, or convulsive episodes with a variable threshold for onset. These seizures, initiated by handling, startling, sudden loud noises, or environmental change, occur in approximately 20–30% of the gerbil population, although the incidence of this genetically influenced trait ranges from near zero to very high. Gerbils are also highly susceptible to cerebrovascular accidents because of their unique cerebral circulation. Anesthetized animals should always be supplemented with oxygen until fully recovered to minimize hypoxemia and central ischemic events.

Ocular Conditions

Gerbils may develop primary conjunctivitis and dacryoadenitis—usually associated with *Rodentibacter* complex, *staphylococcal* infections, or ocular disorders secondary to debilitating systemic disease. Ocular disorders in gerbils often are associated with inflammation, enlargement of the globe or prolapse of the retroorbital Harderian glands. Dust and irritating volatile oils from softwood bedding can also cause increased lacrimation. Gerbils may secrete red porphyrin-containing tears in response to nonspecific stressors (chromodacryorrhea). Anophthalmia also may be seen in some litters.

Genitourinary Conditions

Renal Conditions

Chronic renal failure (interstitial nephritis, tubular nephrosis, glomerulonephropathy) occurs commonly in gerbils older than 1 year of age and is likely related to long-term feeding of inappropriate diets. Gerbils are also susceptible to systemic amyloidosis and may present with nonspecific signs of weight loss, inappetence, and poor hair coat. Pyelonephritis secondary to *C. rodentium* infection, renal cysts, and hydronephrosis has been uncommonly reported. General treatment for renal disease of noninfectious origin is supportive with attempts to reduce protein and phosphorus in the diet.

Infertility

Gerbils are considered monogamous animals, and the loss of a mate may abrogate mating interest in the survivor. Gerbils have a high incidence of reproductive disorders, especially ovarian or periovarian cysts or neoplasms. Granulosa cell tumors often affect both ovaries in the gerbil, and may appear fleshy and lobulated or cystic. Females with large ovarian cysts may be presumed pregnant because of cystic abdominal enlargement. Other causes of infertility in the gerbil include pair incompatibility, sexual immaturity or senescence (older than 18 months), overcrowding, pesticide or other toxin ingestion or absorption, nutritional deficiencies, environmental disturbances, very low temperatures, and various systemic diseases.

Prenatal Mortality

Abortions and stillbirths are difficult to detect because the fetal remains are often buried or consumed. Prenatal deaths may be induced by nutritional deficiencies, systemic or genital disease, trauma, or stress.

Litter Desertion or Death

Approximately 20% of young gerbils do not survive to weaning because of lack of maternal care, lactation failure, suffocation, crushing, or inability to reach or operate feeders or waterers. Maternal neglect or lactation failure may also result from wire-floored or transparent caging, lack of nesting material, lack of water, small litters (1–2 pups), environmental disturbances, presence of an aggressive male, or abnormal or injured young. Loss of an imperfect or threatened litter results in the dam's return to estrus. One of the most common causes of cannibalism among rodents is food or water deprivation.

Sudden Death

Chilling or overheating, septicemia, renal failure, Tyzzer's disease, amyloidosis, starvation or dehydration, neoplasia, and trauma all may cause sudden death in gerbils.

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THE MOUSE

Skin Conditions

Alopecia

Barbering (excessive hair chewing resulting in an appearance of patchy hair loss) is a common observation among cages of mice, particularly among adult female breeding mice (Table 4.17). The muzzle and other areas of the body have the appearance of being shaved closely by cagemates in strain-specific patterns. The behavior is learned and is not necessarily performed by the most dominant animal in the cage. It is more common among females, but both sexes can be involved. When seen, it is usually a sign of overcrowding, social problems requiring regrouping, or a need for increased environmental complexity, including provision of a sufficient amount and different types of nesting material and cage resources that keep animals occupied and permit animals to shelter away from each other. Although usually only superficial hair chewing occurs, occasionally the skin is abraded, which may represent a site of entry for bacteria, leading to abscess or ulcer formation. Barbering of the fur and/or whiskers can also be self-directed. Hair thinning or loss in mice is frequently associated with acariasis (*Myobia musculi, Myocoptes musculinus*, and *Radfordia affinis*), and in some strains, infestation may result in intense pruritus with overgrooming and self-traumatization. Treatment is with ivermectin, selamectin, or moxidectin, although caution should be exercised when using these agents with breeding mice because of the potential for teratogenesis, neonatal toxicity, and interference with transgene expression. Another cause of hair loss is abrasion on feeders or cage tops. Dermatophytosis (*T. mentagrophytes*) is often subclinical or may cause focal hair loss with well-demarcated patches of crusting. Treatment is with oral griseofulvin or either of enilconazole or ketoconazole as a wash. Hereditary hairless and nude (athymic) strains of mice are used in some research applications. Older mice, particularly male mice, may develop rough hair coats and seborrhea.

Swellings and Masses

Abscesses from fighting wounds are common in most mouse strains, are seen more frequently in males, and are most frequently associated with secondary *S. aureus* infection. In some cases, serotypes of this bacterium are similar to those found on the skin of human handlers, suggesting that anthropozoonotic transmission of the bacterium may occur. Cutaneous neoplasia is rare but squamous cell carcinoma has been reported. The incidence of mammary tumors varies by strain of mouse and presence or absence of oncogenic viruses, namely mouse mammary tumor virus. Retrovirus-induced mammary adenocarcinoma occurs with relatively high frequency in older females, and because of the broad distribution of mammary tissue, masses may be found anywhere from the back of the tail, along the sides and ventrum, to the back of the neck. Mammary tumors can be surgically excised but frequently recur and have a poor prognosis. Multicentric lymphoma may present as masses within the cervical, axillary, or inguinal areas.

Low environmental humidity (<20%) has traditionally been thought to cause ringtail, a condition in which one or more annular swellings and then constrictions develop on the tail in association with erythema, edema, necrosis, and sloughing of the distal tissue. Other factors including temperature, dietary deficiencies, genetic susceptibility, and caging type have also been proposed to contribute to this condition. While the etiopathogenesis is unknown, a primary disorder of cornification in mice has recently been suggested based on a retrospective analysis of histologic and environmental data.

Dermatitis

Acariasis, pediculosis (*Polyplax serrata*), and bite wounds are common causes of dermatitis. Severe lice infestations may lead to anemia in younger animals. Allergies to fur mite antigens, exacerbated by self-traumatization, present as highly pruritic lesions on the back, neck, head, and shoulders. These

Table 4.17. Common presenting skin conditions and differential diagnoses in mice.

Condition	Differential Diagnoses
Alopecia	Noninfectious
	Barbering
	Fighting/trauma
	Hereditary hairlessness
	Mechanical, e.g., feeder
	Nutritional deficiencies, e.g., zinc, protein
	Infectious
	Dermatophytosis, e.g., *Trichophyton* spp
	Fur mite infestation, e.g., *Myobia musculi, Myocoptes musculinus, Radfordia affinis*
Swellings/masses	Noninfectious
	Trauma/hemorrhage
	Neoplasia (lymphoma, mammary adenocarcinoma)
	Infectious
	Abscesses, e.g., *Staphylococcus* spp, *Proteus* spp
	Granulomas
	Mastitis
Dermatitis	Noninfectious
	Fighting/bite wounds
	Hypersensitivity
	Gangrenous necrosis from nesting material fibers
	Nutritional deficiencies, e.g., low protein or fat
	Ringtail (low humidity)
	Infectious
	Bacterial, e.g., *Staphylococcus* spp
	Dermatophytosis, e.g., *Trichophyton* spp
	Parasitic, e.g., fur mites (*M. musculi, M. musculinus, R. affinis*), lice (*Polyplax serrata*)
	Viral, e.g., mousepox

lesions range from simple alopecia to small scabs to extensive superficial ulcerative dermatitis, particularly in mice with a C57BL/6 background (black mice) (Figure 4.19). C57BL/6 mice may also develop an idiopathic ulcerative dermatitis. The etiology of this condition is multifactorial, with numerous risk factors described, including genetics, Th1-type immune response, compulsive behavior, diet, sex, age, environmental humidity, season, and fur mite infestation. Idiopathic ulcerative dermatitis lesions typically present on the dorsal intrascapular area, but can occur on the face, neck, head, and elsewhere. Treatments include trimming toenails, topical medication, and supplementation with fatty acids. A necrotic dermatitis caused by an autoimmune vasculitis has been reported in a number of strains and may present as necrosis of the tips of the ears and tail. Bite wounds, common among group-housed male mice, are usually seen on the rump, preputial area, and tail (Figure 4.20). Mice should be picked up regularly and examined thoroughly for signs of fighting and incompatibility. Biting of the preputial or scrotal areas may cause localized preputial and scrotal infections, peritonitis, and even spinal meningitis. Adhesions may develop between the intestines and the scrotal wall. Other causes of dermatitis in mice include mousepox, dietary deficiencies, and dermatophytosis. Infection with ectromelia virus (mousepox), a reportable disease in the United States, may lead to dry



FIGURE 4.19. Severe ulcerative dermatitis on the shoulders and back of a mouse, likely due to a hypersensitivity reaction. Courtesy of I. Phillips.

gangrene and amputation of the distal extremities, if mice are allowed to survive. Gangrenous necrosis of the distal extremities has also been reported in suckling mice when fibers of cotton nesting material used for enrichment become wrapped around their limbs.

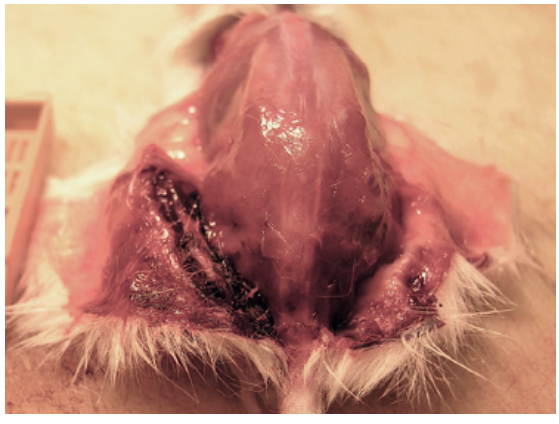


FIGURE 4.20. Necropsy photo of severe bilateral posterior cellulitis that had presented clinically as posterior paresis in a male mouse, induced by fighting. Courtesy of D. Hobson.

Gastrointestinal Conditions

Anorexia

Anorexia occurs frequently in mice and the cause may be difficult to pinpoint. Animals without access to fresh water will not eat. Mice should be monitored closely when new waterers are introduced to ensure that they are able to access and drink from them. Other causes of anorexia include malocclusion of the incisors with consequent difficulty prehending food, pain, neoplasia, and systemic disease (Table 4.18).

Diarrhea

Diarrhea in unweaned mice is often attributable to rotavirus (epizootic disease of infant mice, EDIM), reovirus, or coronavirus (mouse hepatitis virus, MHV) infection. Rotavirus infection may be self-limiting; however, coronavirus infection is often lethal unless enzootic in a colony. The feces are usually yellow and sticky, matting the neonatal hair. Tyzzer's disease; salmonellosis; *C. rodentium*, *Helicobacter* spp., *E. coli*, or *Enterococcus* spp. infection; coccidiosis; giardiasis; spironucleosis; and various dietary factors all may cause diarrhea in mice. Pinworm infestation is common; however, the condition rarely causes clinical signs, even with a high parasite burden. Similarly, mice may be infected with

Table 4.18. Common presenting gastrointestinal conditions and differential diagnoses in mice.

Condition	Differential Diagnoses
Anorexia	Noninfectious
	Dental disease (malocclusion, deformities)
	Insufficient water supply
	Intestinal accident (e.g., volvulus, adhesion, rupture)
	Amyloidosis
	Pain
	Neoplasia
	Infectious
	Secondary to disease—see below
Diarrhea	Noninfectious
	Dietary indiscretion (carbohydrate overload)
	Infectious
	Viral enterocolitis, e.g., coronavirus (mouse hepatitis virus), rotavirus (epizootic diarrhea of infant mice), reovirus Bacterial enterocolitis, e.g., *Citrobacter rodentium*
	L. intracellularis, E. coli, *Salmonella* spp, *Enterococcus* spp, *Helicobacter* spp, *C. piliforme*
	Protozoal infection, e.g., coccidiosis, giardiasis, spironucleosis
Constipation	Noninfectious
	Obesity
	Inappropriate diet (low fiber)
	Lack of exercise
Rectal prolapse	Estrogenic stimulation
	Oxyuriasis, e.g., *Aspiculuris tetraptera*, *Syphacia obvelata*
	Chronic bacterial infection, e.g., *Helicobacter* spp, *C. rodentium*

cestodes (*Rodentolepis* spp. and *Hymenolepis* spp) but clinical signs are rare.

Prolapsed Rectum

The rectum of mice is weakly anchored by the mesocolon and prone to prolapse with straining. Rectal prolapse may be seen with any condition inducing diarrhea, for example, MHV, *Helicobacter* spp., or *Citrobacter* spp. infection, following perianal irritation caused by oxyurid infestation, during pregnancy, or with estrogenic stimulation.

Cardiorespiratory Conditions

Myocardial degeneration and fibrosis are seen relatively commonly at necropsy in older mice; however, clinical disease is rarely noted. Significant epicardial and myocardial mineralization are also seen commonly in some strains of mice, for example, DBA, without apparent clinical effect, and the etiopathogenesis of this condition is unknown. Thrombosis of the auricle can present as left- or right-sided heart failure in mice. The left auricle is most frequently affected. Atrial thrombosis may also extend into the ventricles, cardiac vessels, and pulmonary veins. Atrial thrombosis is often associated with amyloidosis, but is also seen in BALB/c mice, which are not prone to amyloidosis. Left heart failure due to atrial thrombosis is the most common cause of noninfectious dyspnea in mice. Primary pulmonary adenomas and adenocarcinomas are common in mice. Mice vary markedly by strain in their sensitivity to develop pulmonary tumors (e.g., the A and 129 strains are considered highly susceptible, BALB/c intermediate, and C57BL/6 relatively resistant).

Nasal Discharge

Rhinitis may be induced in mice by dust or volatile oils present in softwood bedding (Table 4.19). Bacterial and viral infections often initiate as rhinitis with sneezing and conjunctivitis and may progress to lower respiratory infections and pneumonia depending on the immunocompetence of the mouse and whether there is secondary bacterial infection. Sendai virus, *Mycoplasma pulmonis*, and *Rodentibacter* complex infections are common causes of rhinitis. Less common respiratory pathogens include *K. pneumoniae*, *Corynebacterium kutscheri*, coronavirus infection, and ectromelia virus infection.

Endocrine Conditions

Spontaneous diabetes mellitus has been reported in obese mice fed high-carbohydrate diets, in outbred Swiss mice, and in genetic variants of several strains such as NOD mice. Several spontaneous mutations leading to endocrine disorders have been described in mice. Other spontaneous endocrine conditions are highly unusual. Accessory adrenal cortical nodules are found in periadrenal and perirenal fat, especially in female mice. Some inbred strains have thyrotropic hormone deficiency, resulting in thyroid atrophy. Thyroid cysts lined by stratified squamous epithelium may be seen in aged mice. Amyloid deposition can occur in the thyroid gland, parathyroid glands, and adrenal glands.

Nervous and Musculoskeletal Conditions

Otitis media/interna is commonly seen in mice and may be due to infection with *Rodentibacter* complex, *Streptococcus* spp., or other bacterial agents. Idiopathic vasculitis affecting

Table 4.19. Common presenting cardiorespiratory conditions and differential diagnoses in mice.

Condition	Differential Diagnoses
Nasal discharge/ rhinitis/sneezing	Noninfectious
	Irritation (dust, volatile oils from softwood bedding)
	Infectious
	Bacterial infection, e.g., *Rodentibacter* complex, *S. aureus, Streptococcus* spp
	Viral infection, e.g., Sendai virus
Dyspnea	Noninfectious
	Heat stress
	Primary cardiac disease (cardiomyopathy)
	Systemic disease
	Aspiration pneumonia
	Neoplasia, e.g., lymphoma, pulmonary adenoma
	Infectious
	Bacterial pneumonia, e.g., *Mycoplasma pulmonis*, *Filobacterium rodentium*, *Streptococcus* spp, *Rodentibacter* complex, *S. aureus, K. pneumoniae*
	Viral infection, e.g., Sendai virus

cerebral arteries may also induce otitis interna and incoordination. Bacterial encephalitis and central neoplasia are uncommon; however, trauma from falls may lead to incoordination and seizures, and audiogenic seizures may occur in some strains of mice when exposed to sudden, loud noises. Mice can be carriers of lymphocytic choriomeningitis virus (LCMV) but rarely show clinical signs of disease. Virus may be shed in the urine of asymptomatic mice.

Ocular Conditions

Conjunctivitis occurs commonly in mice and is generally attributable to infection with Sendai virus, *Rodentibacter* complex, *P. aeruginosa, Streptococcus* spp., or *M. pulmonis* infection. Irritation from dusty bedding or volatile oils from softwood bedding, high environmental ammonia levels, and lacrimal gland inflammation may also result in the condition.

Panophthalmitis

Rodentibacter complex is the most common bacterial cause of orbital inflammation in mice, but *Pseudomonas* spp. and LCMV infection may occur also.

Cataracts, Retinal Degeneration, and Congenital Ocular Conditions

Cataracts in mice may be caused by prolonged dessication of the globe, as may occur with surgery or anesthesia, genetic predisposition, and as a consequence of uveitis. Corneal dystrophy is very common in mice and may appear as opacities on the corneal surface. Retinal degeneration frequently develops in albino strains as they age and is caused by exposure to excessive light levels. Some strains such as C3H, CBA, FVB, SJL, and SWR are genetically predisposed to retinal degeneration and thus blindness because they carry the rd gene. Blindness does not typically impact health or reproduction, and blind mice cannot be distinguished from non-blind mice housed in standard caging. Microphthalmia and anophthalmia are inherited characteristics and seen frequently in some strains of mice. In C57BL/6, these lesions are more common in females and in the right eye.

Genitourinary Conditions

Renal Conditions

Renal disease is relatively common in mice and may be associated with infectious causes, such as bacterial cystitis and pyelonephritis in breeding females, usually secondary to *E. coli* or *S. aureus* infection or chronic renal failure in aged rodents of both sexes (Table 4.20). Renal amyloidosis also occurs in older mice and may contribute to renal failure. Renal abscessation occurs sporadically, likely following bacteremia episodes, and renal cysts are generally congenital and incidental in nature. Hydronephrosis may be uni- or bilateral and may be congenital or acquired. Hydronephrosis with hydroureter may occur in aging males due to an ejaculatory plug lodged in the urethra. These animals present with abdominal distension and anorexia and generally have a poor prognosis. The recently discovered mouse kidney parvovirus, also called murine chapparvovirus, is moderately prevalent in laboratory and wild mice. Viral infection results in intranuclear inclusion bodies within the renal tubular epithelium, which were anecdotally noted by veterinary pathologists for more than 40 years in immunocompetent and immunocompromised mice. Clinical disease has only been reported in immunocompromised mice, which may develop chronic renal disease indicated by shrunken, pale, and pitted kidneys.

Reproductive Conditions

Infertility

Reduced fertility or abortion in mice may be caused by chemicals; estrogenic stimulation, for example, phytoestrogens in the diets; inappropriate light cycles; immaturity or senescence; overcrowding; noise; exposure of a pregnant female to the scent of an unfamiliar male (Bruce effect); metritis due to *Rodentibacter* complex, *M. pulmonis, Klebsiella oxytoca*, or *Streptobacillus moniliformis* infections; inbreeding; dichlorvos (used sometimes to treat fur mite infestations); low temperature; and nutritional restriction. Hydrometra due to imperforate hymen will also result in infertility, and breeding pairs producing these offspring should be culled, as the condition is heritable (Figure 4.21). Cystic endometrial hyperplasia and neoplasms such as uterine stromal polyp, leiomyoma, and granulosa cell tumor may occur in older females. Mammary adenocarcinoma is relatively common in mice, and the tumors are caused by retroviral infection (mouse mammary tumor virus). They are generally slow to metastasize. Bacterial orchitis, epididymitis, and preputial gland infection are not uncommon in male mice. Seminal vesicle impaction with massive abdominal distension may be seen in aged males, in addition to testicular tumors.

Litter Desertion or Death

Mouse litters are abandoned or destroyed if nests are inadequate, the litter is small, the pups are injured or abnormal, the dam is malnourished resulting in agalactia, the nest or young are disturbed or handled, or the young become dehydrated or cold because of inadequate nest material, humidity, or temperature. A variety of environmental disturbances, such as high-pitched sound associated with cage washers and steam hoses, may cause maternal distress and litter abandonment. One of the most common causes of death in suckling mice is an epizootic MHV infection. Other pathogens, such as salmonella or rotavirus, can also affect maternal and litter health.

Uterine prolapse is uncommon but may follow dystocia or abortions of large fetuses.

Sudden Death

Mice may die unexpectedly from dehydration, lack of access to feed, sudden environmental stressors, or shock resulting in massive thymic involution or gastrointestinal hemorrhage,

Table 4.20. Common presenting genitourinary conditions and differential diagnoses in mice.

Condition	Differential Diagnoses
Renal conditions	Noninfectious
	Chronic renal failure
	Hydronephrosis
	Urethral obstruction, e.g., ejaculatory plug
	Amyloidosis
	Renal cyst
	Neoplasia, e.g., lymphoma
	Infectious
	Pyelonephritis/nephritis/cystitis secondary to bacterial infection, e.g., *S. aureus, E. coli*
	Renal abscess
Uterine/ovarian conditions	Noninfectious
	Cystic endometrial hyperplasia
	Hydrometra (imperforate hymen)
	Infertility, e.g., inadequate protein or fat, inappropriate light cycle, senescence, immaturity, low ambient temperature
	Abortion, e.g., stress, hyperthermia, trauma
	Neoplasia, e.g., uterine stromal polyp, leiomyoma, granulosa cell tumor, teratoma
	Infectious
	Pyometra/metritis following bacterial infection, e.g., *P. multocida, S. aureus*
Mammary gland conditions	Noninfectious
	Neoplasia
	Infectious
	Mastitis, e.g., *S. aureus*
Male reproductive conditions	Noninfectious
	Trauma
	Seminal vesicle impaction
	Neoplasia
	Infectious
	Preputial gland abscess
	Orchitis and epididymitis following fighting injury and bacterial infection

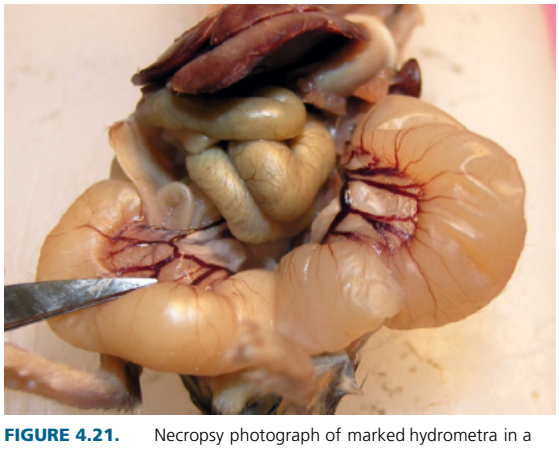


FIGURE 4.21. Necropsy photograph of marked hydrometra in a female mouse. This animal had marked abdominal distension ante mortem. Courtesy of D. Hobson.

heat stress, trauma, urolithiasis in males, organophosphates, chronic renal disease, septicemia, and toxemia. Sendai virus (extremely rare) and MHV (highly common) are particularly insidious killers of mice. Fighting and social incompatibility with resultant starvation may also result in death of subordinate animals.

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THE RAT

Skin Conditions

Alopecia

Hair loss or thinning without dermatitis is seen in some strains of rats, and hair loss may occur with accompanying dermatitis (Table 4.21). Dermatophytosis, abrasion on cages or bedding, and mutual grooming or barbering all produce hair loss with little or no grossly evident dermatitis.

Swelling and Masses

The most common subcutaneous masses in female rats are mammary tumors, a fibroadenoma in most cases, although adenocarcinomas do occur (Figure 4.22). These tumors may grow to become very large and can be removed surgically. Ovariohysterectomy is often curative, although tumors may still arise in neutered animals with prolactin-secreting pituitary adenomas. Other types of neoplasms do occur, such as fibrosarcoma, squamous cell carcinoma of the head, and rarely thyroid and salivary gland tumors. Auricular chondritis and Zymbal's gland tumors (classified as adenomas or adenocarcinomas, depending on the histologic appearance) occur commonly in some strains of rats (Figure 4.23). Tumors of the Zymbal gland, a sebaceous gland found in proximal aspect of the external ear canal, should be considered as a differential for unilateral otitis externa in rats. *S. aureus, Rodentibacter* complex, and *K. pneumoniae* abscesses occur uncommonly, as do arthropathies from *Streptobacillus* spp. and *Erysipelothrix* spp. infections. Cervical swelling may result from salivary gland inflammation, secondary to sialodacryoadenitis virus

Table 4.21. Common presenting skin conditions and differential diagnoses in rats.

Condition	Differential Diagnoses
Alopecia	Noninfectious
	Fighting/trauma
	Barbering
	Mechanical, e.g., feeder
	Nutritional deficiencies
	Infectious
	Dermatophytosis, e.g., *Trichophyton* spp
	Mite infestations, e.g., *Radfordia ensifera, Notoedres muris*
Swellings/masses	Noninfectious
	Trauma/hemorrhage
	Neoplasia (mammary fibroadenoma, lymphoma, fibrosarcoma, Zymbal's gland carcinoma, squamous cell carcinoma)
	Infectious
	Abscesses, e.g., *Staphylococcus* spp, *Rodentibacter* complex
	Granulomas
	Mastitis
Dermatitis	Noninfectious
	Fighting/bite wounds
	Nutritional deficiencies, e.g., low protein
	Rough bedding
	Ringtail (low humidity)
	Infectious
	Bacterial, e.g., *Staphylococcus* spp
	Dermatophytosis, e.g., *Trichophyton* spp
	Parasitic, e.g., mites (*Notoedres* spp, *Demodex* spp), lice (*Polyplax spinulosa*)



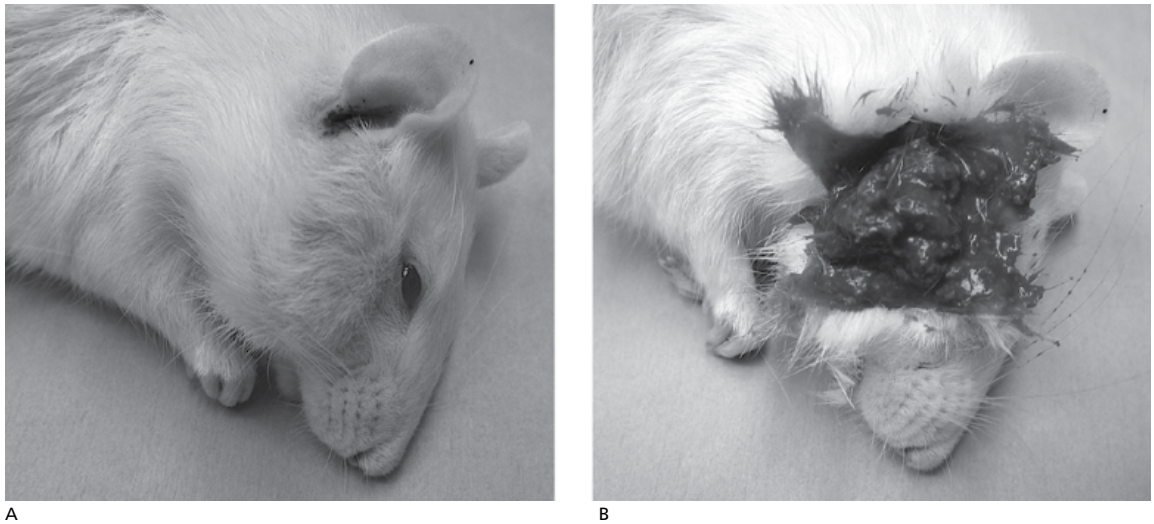
FIGURE 4.22. Mammary gland fibroadenomas in aged sibling female rats.

infection or multicentric lymphoma. *S. aureus* and *Rodentibacter* complex may cause mastitis.

Swelling and dry gangrene of the tail are sometimes seen in infant mice and rats exposed to low humidity or low temperatures. The tail is used for thermoregulation in rats and mice, and either of these environmental conditions may lead to shunting of blood away from the tail with subsequent ischemic necrosis. The condition presents as annular swellings around the tail vertebrae, lending it the common name of ringtail. Mild forms of the condition are reversible by adjusting environmental conditions if caught early in the process. Ringtail may occur in young preweaned rat pups, as in mice (see above). The etiology of the condition has not been determined, although low ambient temperatures and relative humidity have been thought to contribute to the condition. Lanolin cream applied to early lesions once daily for at least six days may prevent further deterioration and necrosis.

Dermatitis

S. aureus, *Polyplax spinulosa*, and *T. mentagrophytes* are implicated occasionally as causative agents of rat dermatitis. *Ornithonyssus bacoti*, the tropical rat mite, is rare but has been reported in animals obtained from pet stores and occasionally in rats and mice housed in research facilities, following wild rodent incursions. *O. bacoti* has been shown to experimentally harbor and transmit a variety of human diseases, some of which are reportable, such as Tularemia (*F. tularensis*) and Q fever (*Coxiella burnetti*). Infestation with *O. bacoti* may first be detected following development of pruritic papular



A B

FIGURE 4.23. Facial swelling in a Fischer 344 rat at necropsy (A). Mass opened to demonstrate a Zymbal's gland carcinoma (B), a common neoplasm in aged F344 rats. Courtesy of L.B. Martin.

dermatitis in individuals handling rats, known as rat mite dermatitis. Pruritis with secondary *S. aureus* infection may result in ulcerative lesions on the neck and anterior trunk that are difficult to treat. Trimming the hind nails, topical treatment with zinc ointment, and administration of long-acting penicillin subcutaneously may help to resolve the condition. Infestation with the mite *Notoedres muris* may lead to a permanent and disfiguring auricular chondritis. *S. aureus* may also induce a gangrenous pododermatitis in colonies, which can be difficult to manage. Serotypes of the bacteria are often identical to those found on the skin of human handlers, suggesting that anthropozoonotic transmission of this bacterium may occur. Fighting wounds are seen less commonly in group-housed rats of either sex but when present often occur on the side of the face or flank. This may present first as small areas of patchy alopecia with rare wounds and crusts. Pododermatitis may be seen in rats housed on coarse or wet bedding, or when housed for prolonged periods of time on wire-bottom cages. Tail slip, as described for gerbils, may occur in rats when they are picked up by the distal third of their tail. Treatment is as described for gerbils.

Gastrointestinal Conditions

Gastrointestinal disease is uncommon in rats. Malocclusion may occur from incisor overgrowth, leading to excess salivation and inability to prehend food. Diarrhea associated with rotavirus infection has been reported in suckling rats but is generally mild and self-limiting. Tyzzer's disease with associated typhlitis is reported rarely in rats, although rats are common carriers of the bacterial spore. Pinworm (*S. muris, A. obvelata*) and cestode (*R. nana, Hymenolepis* spp) infections are generally subclinical, even in the face of high parasite burdens.

Cardiorespiratory Conditions

Rhinitis

Sniffling, sneezing, and serous nasal discharge are associated with respiratory mycoplasmosis commonly in companion rats and less commonly with infection by *C. kutscheri*, *Rodentibacter pneumotropicus*, *S. pneumoniae, S. zooepidemicus*, and sialodacryoadenitis virus (coronavirus) infections (Table 4.22). A red ocular and nasal discharge (chromodacryorrhea), rich in lacrimal lipids and fluorescent porphyrins of Harderian gland origin, accompanies many debilitating diseases and other conditions inducing stress in rats (Figure 4.24).

Dyspnea

Myocardial fibrosis and degeneration may be seen commonly in older rats and may result in pulmonary edema and sudden collapse.

Pneumonia in rats, often precipitated by ammonia-laden environments or under stressful or otherwise debilitating conditions, can be caused by *M. pulmonis*, *Filobacterium rodentium, S. pneumoniae*, and *Rodentibacter* complex. Less often *C. kutscheri, Aspergillus* spp., *S. equi* supsp. *Zooepidemicus*, and *Haemophilus* spp. are involved. Uncomplicated Sendai virus infection can cause death in pregnant or aged rats. These rats develop rough hair coats and dyspnea but not rhinitis. The potential for several other emerging and newly characterized rodent paramyxoviruses primarily reported from Asia to infect laboratory and companion rats is unknown. *Pneumocystis carinii* has been described in rats in

Table 4.22. Common presenting cardiorespiratory conditions and differential diagnoses in rats.

Condition	Differential Diagnoses
Nasal discharge/ Rhinitis/sneezing	Noninfectious Irritation (volatile oils from softwood bedding) Nasal foreign body Infectious Bacterial infection, e.g., *M. pulmonis*, *Filobacter rodentium*, *S. pneumoniae, Corynebacterium kutscheri* Fungal, e.g., aspergillosis associated with corncob bedding, *Pneumocystis carinii* Viral, e.g., SDAV
Dyspnea	Noninfectious Heat stress Primary cardiac disease (myocardial degeneration) Systemic disease Aspiration pneumonia Esophageal foreign body (choke) Neoplasia, e.g., lymphoma with chylothorax, pulmonary adenoma Infectious Larval migration through lungs Bacterial pneumonia, e.g., *C. kutscheri*, *Streptococcus* spp, *Rodentibacter spp., S. aureus, K. pneumoniae* Viral infection, e.g., Sendai virus



FIGURE 4.24. Bilateral chromodacryorrhea in a rat. This is a nonspecific sign of stress in many rodents.

North America and Europe. Affected animals may have no clinical signs but may die suddenly under anesthesia. Gross lesions consist of random, multifocal 1–4 mm flat to raised pale to plum-colored foci on the surface of the parenchyma. The lesion resolves in older animals leaving only perivascular lymphoplasmacytic cuffing and multifocal alveolar macrophage aggregates.

Chylothorax has been reported infrequently in rats and is associated with dyspnea. *Trichosomoides crassicauda*, a nematode that infects the urinary bladder of rats, may be associated with dyspnea and lung lesions during the time that larvae migrate through the lungs. Pulmonary adenoma is reported in aged rats.

Endocrine Conditions

Pituitary gland hyperplasia and adenomas are common in aging rats of certain strains and are generally slow-growing, space-occupying masses that will eventually lead to neurologic signs such as seizures, head tilt, and paresis. Thyroid tumors (C cell origin) are common in older rats, although they are rarely clinically important. Pancreatitis with destruction of pancreatic islets and resultant diabetes mellitus has been reported rarely in rats. Pancreatic islet cell tumor also occurs infrequently in older animals.

Nervous and Musculoskeletal Conditions

Head Tilt

Otitis media/interna, pituitary adenoma, and encephalitis may cause head tilt in rats. Otitis caused by *M. pulmonis, S. moniliformis, Streptococcus* spp., and *P. aeruginosa* have all been reported (Table 4.23).

Table 4.23. Common presenting nervous and musculoskeletal conditions and differential diagnoses in rats.

Condition	Differential Diagnoses
Head tilt/torticollis	Noninfectious
	Trauma
	Cerebrovascular accident
	Toxins, e.g., lead (paint)
	Neoplasia, e.g., pituitary adenoma
	Infectious
	Otitis media/interna secondary to bacterial infection, e.g., *M. pulmonis, S. aureus*
	Brain abscess
Seizures	Noninfectious
	Heat stroke
	Hypoxia
	Audiogenic seizure
	Severe systemic disease
	Neoplasia
	Infectious
	Bacterial encephalitis/meningitis/abscess, e.g., *Streptococcus* spp
Paresis/paralysis	Noninfectious
	Trauma (leg/muscle)
	Fractures
	Osteoarthritis
	Degenerative disease, e.g., polyradiculoneuropathy
	Severe inanition
	Neoplasia, e.g., lymphoma, vertebral histiocytic sarcoma, pancreatic islet cell tumor (weakness, incoordination)
	Infectious
	Spinal abscess

Incoordination and Seizures

Trauma, encephalitis, pituitary neoplasia, severe systemic disease, wasting, and otitis interna can lead to incoordination in rats. Pancreatic islet cell tumor may lead to clinical signs of ataxia following pulsatile release of insulin with resulting hypoglycemia.

Paresis or Paralysis

Brain or spinal lesions (e.g., abscesses, phycomycosis, or neoplasia), trauma of the spinal cord, malnutrition, polyradiculoneuropathy, and osteoarthritis can produce limb weakness or paralysis.

Abscesses at the head of the tail or in the perineum may extend into the spinal canal, resulting in myelitis.

Ocular Conditions

Chromodacryorrhea

Localized bacterial infections and sialodacryoadenitis virus produce blepharospasm, swelling, lacrimation, and sometimes a mucopurulent discharge. Red tears or chromodacryorrhea is a nonspecific sign of stress or underlying disease. The red pigments in tears are protoporphyrin IX and coproporphyrin III, synthesized de novo in the Harderian gland and expelled under parasympathetic discharge. The pigments are identified in dried tears by the orange-red fluorescence under ultraviolet light. The eyelids, nares, and forepaws may be smeared with the pigment. Unilateral involvement probably indicates atrophy of the secretory cells of one Harderian gland or blockage of a nasolacrimal duct.

Conjunctivitis

Conjunctivitis in rats with swelling and discharge may be caused by *Rodentibacter* complex, *S. pneumoniae*, sialodacryoadenitis virus (SDAV), self-trauma, or dust or ammonia irritation. Conjunctivitis may be associated with other primary ocular diseases, including keratoconjunctivitis, uveitis, glaucoma, and corneal opacity. Hypovitaminosis A and SDAV are causes of keratoconjunctivitis.

Dacryoadenitis

Inflammation of the lacrimal glands is related to SDAV or rarely to bacterial infection of the glands.

Other Conditions

Corneal dystrophy is common in rats and is heritable. Corneal hypoxia, as occurs with certain injectable anesthetic agents, may lead to keratitis and ulceration. Supplemental oxygen, reversible anesthetic injectable agents, and sterile eye lubrication should always be used in rats to enhance postanesthetic recovery time and minimize the occurrence of this condition. Exophthalmos from Harderian gland enlargement (e.g., due to SDAV infection) can occur, as can microphthalmia.

Genitourinary Conditions

Renal Conditions

Chronic progressive nephrosis, also called chronic progressive nephropathy, is a common life-threatening condition of older rats and is related to male sex, ad libitum feeding, age, and strain, for example, Sprague-Dawley rats (Table 4.24). Nephrocalcinosis is common in certain strains of rats and is more frequently seen in females as young as 7 weeks of age. Urolithiasis (commonly struvite) has been reported sporadically in rats fed normal diets (Figure 4.25). Hydronephrosis may be unilateral or bilateral and congenital or acquired in origin. Congenital hydronephrosis is often an incidental finding at necropsy, as are solitary renal cysts and renal polycystic disease. Acquired hydronephrosis may result from an ascending suppurative pyelonephritis and cystitis, commonly caused by *E. coli* or *Proteus* spp. infection.

Reproductive Conditions

Infertility

Rats younger than 70 days or older than 18 months of age may be sexually incompetent. Other causes of real or apparent infertility include vitamin E deficiency, protein deficiency, viral infection, for example, caused by Sendai virus, sialodacryoadenitis, rat virus, *M. pulmonis*—related metritis, elevated temperature and humidity, constant light, and systemic

Table 4.24. Common presenting genitourinary conditions and differential diagnoses in rats.

Condition	Differential Diagnoses
Renal conditions	Noninfectious Chronic renal failure Polycystic kidney disease Urolithiasis Hydronephrosis Neoplasia, e.g., lymphoma Infectious Pyelonephritis/nephritis/cystitis secondary to bacterial infection, e.g., *Proteus* spp, *E. coli* Septicemia Renal abscess
Uterine Conditions	Noninfectious Cystic endometrial hyperplasia Infertility, e.g., inadequate protein or vitamin E content, inappropriate light cycle, senescence, immaturity, mate incompatibility, low ambient temperature Abortion, e.g., stress, hyperthermia, trauma Neoplasia, e.g., leiomyoma Hydrometra Infectious Pyometra/metritis following bacterial infection, e.g., *P. multocida, S. aureus*
Mammary Gland Conditions	Noninfectious Neoplasia Infectious Mastitis, e.g., *S. aureus*
Male Reproductive Conditions	Noninfectious Trauma Neoplasia Infectious Bacterial infection, e.g., prostatitis

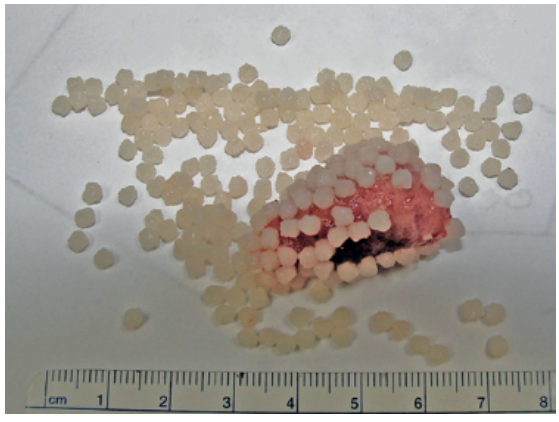


FIGURE 4.25. Uroliths from the urinary bladder of an 8 week-old female rat. Generally, animals have 1–10 stones; however, this case was somewhat unusual in that 266 stones were recovered. The urolith composition was largely calcium carbonate. Courtesy of K. Pucaj.



FIGURE 4.26. Vaginal prolapse in a female rat.

disease. Vaginal prolapse may be seen rarely (Figure 4.26). Bacterial prostatitis may be seen in older males and cystic endometrial hyperplasia occurs in older female rats.

Litter Desertion or Death

Factors that may lead to destruction of neonates include excessive environmental noise, deformed or dead young, overcrowding, injured young, presence of the male parent, a small litter, dirty cage, lack of privacy, lack of nesting material, and agalactia.

Sudden Death

Adult rats can die from inapparent pneumonia, chronic renal failure, overwhelming neoplasia, sudden shock, or stress with massive thymic or gastrointestinal hemorrhage, lack of water, overheating or chilling, and ileus following intraperitoneal administration of certain chemicals (e.g., chloral hydrate).

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Table 4.25. Summary of zoonotic conditions reported for rabbits and rodents.

Agent	Species Affected
Viral disease	
Lymphocytic choriomeningitis virus	Hamsters, guinea pigs, mice
Rabies virus	Rabbits, guinea pigs
Hantavirus	Rats, mice
Hepatitis E virus	Rabbits
SARS-CoV-2 virus	Hamsters
Bacterial disease	
Chlamydia caviae	Guinea pigs
Francisella tularensis	Rabbits, hamsters
Salmonella spp	Rabbits, guinea pigs, chinchillas, hamsters, mice, rats
Caviibacter abscessus, Streptobacillis moniliformis	Guinea pigs, rats, mice
Spirillum minus	Rats, mice
Rodentibacter complex	Mice, rats, hamsters, gerbils
P. multocida	Rabbits, guinea pigs
S. pneumoniae	Rats, guinea pigs
Campylobacter spp	Hamsters
Yersinia spp	Rabbits, wild rodents
Leptospira spp	Rats, mice
Fungal disease	
Trichophyton mentagrophytes	All
Protozoal disease	
Cryptosporidiosis	All
Encephalitozoon cuniculi	Rabbits
Parasitic disease	
T. caviae	Guinea pig
Hymenolepis spp/*Rodentolepis* spp	Hamster, gerbil, rat, mouse

Summary of Zoonotic Conditions of Companion Rabbits and Rodents

The following table (Table 4.25) does not summarize all possible agents that may be contracted from wild or feral rabbits and rodents, but rather those that may be transmitted largely from conventionally sourced companion rabbits and rodents. Risk of animal infection with certain conditions increases with increased time that animals spend outdoors as well as time in potential contact with various domestic animals, such as cats and pigs as well as wild rabbits and rodents. Risk of human exposure increases for those sheltering or working directly with wild rodents and rabbits, hunting and dressing carcasses of rabbits and various rodents, working in meat rabbit abattoirs, working in small mammal or exotic animal shelters and distribution centers, and working in wildlife rehabilitation centers.

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Chapter 5

Specific Diseases and Conditions

This chapter describes selected diseases and conditions prevalent in companion and laboratory rabbits and rodents, fur or meat rabbits, and of importance to biomedical research and public health. This listing is not complete. Tuberculosis, yersiniosis, mycotic infections other than dermatophytoses, many viral diseases, congenital abnormalities, and several nutritional conditions are referenced in Chapter 4 but are not described further. References in this chapter are included at the end of each discussion of a disease or condition. Differences in normal flora, housing and management conditions, and diet result in significant differences in disease incidence in rabbits and rodents housed as companions, for food or fur production, or worked with in research. A major difference between research rabbits and rodents and companion animals of the same species is life span. The companion rabbit or rodent tends to live much longer than does the research animal, and the companion will exhibit many more diseases and conditions that accompany aging. For example, most rabbits raised for meat are shipped at less than 5 months of age and most laboratory rabbits are younger than 3 years of age, whereas rabbits kept as companion animals may live 5–12 years. Companion rodents also tend to be more prone to husbandry-related conditions and nutritional diseases than rodents kept in biomedical research facilities. Production animals are more likely to contract diseases associated with high-energy diets and high-prevalence infectious diseases. Laboratory animals typically live in conditions that exclude most of the more common diseases; congenital and hereditary conditions are therefore more likely to be seen. Experimental conditions resulting in immunodeficiency may predispose animals to opportunistic diseases, and the experimental conditions themselves can result in iatrogenic disease.

ACARIASIS (MITE INFECTIONS)

General Discussion

Hosts

In general, most mite species affecting rabbits and rodents are host-specific; however, some, such as *Cheyletiella* spp., are freely contagious from one host species to another and can also transiently infest humans. Bites on nondefinitive hosts are generally not adaptive behavior for the mite, as other species usually represent accidental or dead-end hosts, which don't support species reproduction.

Etiology

Mites are small arachnids, similar to scorpions and spiders, and as adults, they have four pairs of legs and two body parts instead of three pairs of legs and three body parts, as seen on insects.

Transmission

Most mites of laboratory animals spend their entire life cycle on one host. Anatomic adaptations and feeding requirements confine mites to the host unless they are brushed onto the bedding or leave because of overpopulation or death of the host. Direct transfer from adult to suckling young is the most common route of spread. Mites are also spread by direct contact with infested hosts, pelage, debris, or bedding. Mites off the host usually die within 3 weeks. When laid, ova are attached either to hair shafts near the epidermis (surface-dwelling mites), or are laid in epidermal tunnels (burrowing mites), and hatch approximately four days after being deposited. Ova are resistant to environmental factors and may survive for long, indefinite periods off the host.

Predisposing Factors

Clinically apparent mite infections in debilitated or chronically diseased older hosts, in young hosts, or in animals housed in unsanitary or stressful environments are often more severe

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than infections in more vigorous individuals. This may be due to variations in self-grooming behavior or a suppressed immune response. Healthy infected animals in enzootically infected colonies become immune, and the mite population will begin to decline when the animals are 2–3 months of age. Introduction of new susceptible hosts into a colony at this time, that is, suckling young, weanlings, or new animals, will allow the cycle to continue. Through their pheromones, companion and laboratory rodents attract feral or wild rodents of like species. This contact provides an ideal opportunity for transfer of many infections and parasites, including mites.

Diagnosis

Ectoparasites can be diagnosed in rodents and rabbits in many ways, and they persist in numerous colonies and individual animals because they continue to be challenging to detect and control. Only a few methods of detection are covered here. In the live animal, adult mites, such as the rabbit ear mite, can sometimes be seen moving on the host with the unaided eye. Loupes or a hand lens can be used to examine the fur, especially around the head, ears, neck, perianal region, and margins of lesions. A piece of filter paper placed within a vacuum hose will collect skin debris, including surface-dwelling mites, upon vacuuming the animal's body. The debris is transferred to a pool of mineral oil on a microscope slide and examined for eggs and parasites. The pelage can be brushed or combed over a dark background and the background examined for ectoparasites. The collected material is then examined carefully with a hand lens for live mites or picked up with clear cellophane tape and examined microscopically. Clear cellophane tape can also be applied directly to the skin or fur to pick up debris, or a scalpel blade dipped in mineral oil can be used to take deep skin scrapings. Material is transferred to a microscope slide, a cover slip is placed on the slide, and it is examined microscopically for ova and mites (Figure 5.1). Skin biopsies of a mite-induced lesion may reveal hyperkeratosis, acanthosis, cutaneous ulcers, scabs, crusts, and secondary bacterial colonization. Sectioned profiles of mites and their eggs may also be seen. Lack of visual detection by one of the above means does not rule out infestation.

When the host dies or is killed, the parasites migrate off the cool pelt and move toward the warmer tips of the hair. Cellophane tape can be applied to the fur and then placed on a glass slide and examined. If the pelt is placed on dark-colored paper surrounded by a frame of either double-gummed cellophane or packing tape or a bead of petroleum gel for several hours, the mites become trapped as they leave the pelt and try to cross the tape or gel.

More recently, PCR tests have become commercially available for assaying for common rodent fur mites (*Myocoptes musculinus*, *Radfordia affinis*, *Myobia musculi*) and are conducted by swabbing the fur or cage (i.e., environmental) testing the filter top, filter from the exhaust plenum, or filter media placed in soiled cages, if animals are housed in microisolator cages, or by fecal analysis (see Chapter 3). These molecular assays are highly sensitive, specific, and reliable but may occasionally yield false positive results when used on animals after treatment, as they don't distinguish between active infections with live mites and past infections with remaining mite debris.

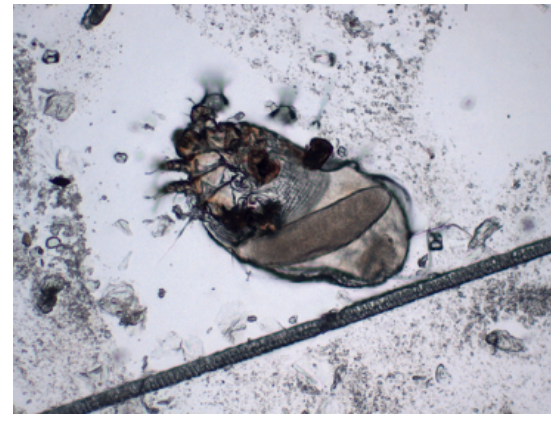


FIGURE 5.1. Gravid female fur mite from a mouse collected using cellophane tape method.

Treatment

Treatments effective in one species of rodent are likely effective in others, with appropriate adjustments in dose based on body weight. Mites, once established in a colony, were more realistically controlled rather than eliminated before the advent of ivermectin, selamectin, and moxidectin. These drugs in the macrocyclic lactone family, a potent group of systemic parasiticides many of which were originally derived from *Streptomyces* spp., have a broad spectrum of action against many arachnids and nematodes. These chemicals have specific actions in invertebrate muscles and nerves and generally have a wide margin of safety in mammals because of a low affinity for similar receptor targets in mammals. These therapeutic agents do not readily cross the blood–brain barrier, though some breeds or strains with an incomplete blood–brain barrier develop neurological signs following application of recommended therapeutic doses. Treatment with pyrethrins or organophosphates can also be successfully employed.

Silicate dusts, alone or compounded with insecticides, abrade, and desiccate ectoparasites and provide a mechanical alternative to potentially toxic chemicals. This material is mixed with contact bedding in the affected animals' cages.

With research animals, the consequences of treatment of ectoparasitism on subsequent use of the animals must be carefully evaluated to ensure the animals are not rendered unusable. Reproduction, transgene expression, and animal behavior may be altered by such treatments. People must be protected from excessive exposure to the products used in treatment. Appropriate drug withdrawal times must be observed for rabbits being shipped for food consumption.

Elimination of ectoparasites from the premises requires treatment and removal or containment of all possible host animals, thorough mechanical scrubbing of the environment, and, in severe cases, fumigation of the room with hydrogen peroxide or formaldehyde gas generated from paraformaldehyde. Fomites such as feed bags, carts, waste containers, and clothing and notebooks moved from room to room also must be cleaned to remove ectoparasites. Rooms should be repopulated with animals proven free of ectoparasites.

Prevention

In research facilities, mite infestations are prevented by placing clean stock into clean premises and using dedicated equipment in animal rooms. Potentially infected animals should be separated, quarantined, and treated until determined to be free of infection, and the premises should be disinfected. Wild rodents must be excluded from the colony or housing room.

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Acariasis in the Rabbit

Etiology

Fur mites are commonly found on companion, meat, and wild rabbits. Mites found on rabbits are usually members of the suborder Prostigmata, superfamily Cheyletidae. Commonly encountered rabbit mites include *Psoroptes cuniculi*, the rabbit ear mite (ear canker) (Figures 5.2 and 5.3), and *Cheyletiella parasitovorax* (walking dandruff) (Figure 5.4), a surface-dwelling fur mite that lives on the keratin layer of the skin and that has a broad host range, including guinea pigs, chinchillas, dogs, cats, and humans. *Leporacarus gibbus*, another fur mite, is less common but seen occasionally in both companion and research rabbits and may occasionally induce



FIGURE 5.2. Heavy infestation of *Psoroptes cuniculi* (arrows) in a rabbit ear as seen using a pediatric otoscope.



FIGURE 5.3. *P. cuniculi* infestation in a rabbit before (left) and after (right) cleaning. Courtesy of Calgary Avian & Exotic Pet Clinic.



FIGURE 5.4. *Cheyletiella parasitovorax* infestation in a rabbit. Flaky, scaling skin is seen commonly in conjunction with this mite.

dermatitis and pruritis in other companion animals, such as cats, that share the same household. Ear mite infections have the potential to cause significant economic loss in meat-producing animals if not treated and controlled, and severe infestations may interfere with normal behaviors such as eating, drinking, and ambulating.

Demodex cuniculi mites reside in hair follicles. There have been only a few reports of *Demodex* spp. in rabbits. Their presence is usually not associated with clinical signs. *Notoedres cati* and *Sarcoptes scabiei* are nonspecies-specific burrowing mites that rarely affect pet or research rabbits. *S. scabiei*, a burrowing mange mite, can cause intense pruritus and dermal lesions of the head and neck.

Transmission

The egg-to-egg life cycle of *P. cuniculi* requires approximately 21 days. The entire life cycle of *C. parasitovorax* takes place on the animal and requires approximately 35 days.

Clinical Signs

In rabbits, the nonburrowing *P. cuniculi* mites chew and pierce epidermal layers of the pinnae of the ear, inducing an inflammatory response and resulting in characteristic accumulations of multiple layers of thin, tan, flaky crust in the external ear canal. The mites are seen rarely on the skin of the adjacent head and throat or almost any other part of the body. Beneath the crusts the skin is hairless, moist, and raw. Secondary bacterial infections, though uncommon, may cause scratching, head shaking, and head tilt if there is an accompanying unilateral bacterial otitis media. Extension of an uncomplicated mite infection to the middle and inner ears is not reported.

C. parasitovorax may not cause clinical signs in rabbits, or infestation may result in loose hair that can be pulled out in clumps. Affected skin may be slightly reddened, oily, hairless, and scaly in patches over the back, shoulders, and head. Rabbits with *Cheyletiella* mite infestations appear to have increased "dandruff" on the skin and deep in the fur.

The small *L. gibbus*, also a surface-dwelling fur mite of rabbits, is nonpathogenic even though it can be present in large numbers. *L. gibbus* is found predominantly on the abdomen and back of rabbits.

Diagnosis

In early or light infections, *Psoroptes* mites and lesions are deep in the concha or external ear canal and are easily overlooked. *P. cuniculi* mites are readily seen with a pediatric otoscope or an endoscope (Figure 5.2). The mites move rapidly in the external ear canal, and they are large enough to be seen with the unaided eye, although frequently they are covered with debris. Examination of debris scrapings (in mineral oil) from the ear canal reveals round-to-oval mites with well-developed legs and bell-shaped suckers on the ends of the first and second pairs of legs of the female mite. Refractory cases should include a complete work-up with clear identification of the parasite. *S. scabiei* mites may rarely be found infesting the ears of rabbits, inducing an intensely pruritic dermatitis with superficial canal and external ear crusting. This mite can only be identified with deep skin scrapings and the treatment is different than for *P. cuniculi*, making definitive diagnosis all the more critical.

In the case of *C. parasitovorax* infections, examination of the fur may reveal pale yellow-to-white mites, approximately 0.3 mm long, with piercing chelicerae and large, curved papal hooks.

Treatment

In uncomplicated infestations of *P. cuniculi*, the mite can be eliminated (smothered) with mineral oil or oil-based insecticide preparations. One or 2 mL of the liquid preparations are massaged into each ear canal. The ear drum must be intact if using this technique. Acaricides are usually not ovicidal, and treatment is repeated approximately 7–14 days later to eliminate recently hatched immature mites before they can deposit ova. This should always be accompanied by an in-depth environmental clean-up at home or in the vivarium or barn.

Ivermectin (200–440 µg/kg, SC or IM) given every 7–18 days for three treatments has eliminated all *P. cuniculi* mites in several studies and appears to be safe for rabbits (note: ivermectin is not approved for meat rabbits). The 1% cattle formulation was used in a number of these studies. Ivermectin should not be used in rabbits intended for human consumption because of the potential for drug residues in major organs. Two 400 µg/kg doses given subcutaneously 7–14 days apart were also clinically effective and eradicated the infection. Ivermectin persisted in the skin of the body and ears long enough (9 and 13 days, respectively) to remove the new generation of mites as they hatched from ova. Also, at this dose, the maximum plasma concentration of 42 ng/mL was achieved approximately two days postinjection; however, the biological half-life in rabbits is not known, and ivermectin lacks ovicidal properties. Most current reports recommend treating at least twice at a 2- to 3-week interval.

Dermatitis has been described on the hind quarters above the tail due to *P. cuniculi* infection. After clipping and scrubbing with an iodine preparation, the area was treated twice per

day with a topical application of Panalog®, an antimicrobial-steroid ointment, prior to treating the mites.

More recent studies evaluating the activity of other macrocyclic lactones, such as selamectin and moxidectin, against *P. cuniculi* and *Sarcoptes scabei* suggest that topical selamectin administered to the skin at the base of the neck of New Zealand white rabbits at a dose of 6–18 mg/kg either as a single dose or repeated at a 4-week interval is safe and efficacious in treating and removing all *P. cuniculi* and *S. scabei* mites. Moxidectin at 0.2 mg/kg given in two oral doses 10 days apart was very effective at eliminating *P. cuniculi* infestations in rabbits. Topical moxidectin spot-on is also safe and efficacious.

In severe cases, rabbits with swollen and painful ears may need to be provided with an analgesic, such as meloxicam or carprofen while swelling and lesions subside.

Cheyletiella spp. can be eliminated by treating rabbits topically with a single dose of selamectin at 12 mg/kg. Complete resolution of *Cheyletiella* infestation was noted up to 5 weeks posttreatment. Ivermectin injections (SC) at 200–450 µg/kg given 2–3 times at 10–21 day intervals have been shown to be similarly efficacious in treating *C. parasitovorax* infestations in rabbits.

Selamectin administered topically at the base of the neck at a dose of 10–12 mg/kg was only partially effective at killing sarcoptic mange mites in Angora rabbits. Doramectin 1% given at 0.2 mg/kg SC following two injections of moxidectin 1% at 0.2 mg/kg given 2 weeks apart was very effective at eliminating *S. scabiei* from the ears of Angora rabbits.

Prevention

Newly arriving rabbits, unless known to be free of ear mites, should be quarantined and treated twice with ivermectin at 400 µg/kg body weight SC at a 14-day interval or selamectin topical applied at 6–18 mg/kg at a similar interval before being placed in an established clean colony. New introductions, whether companion, breeder, or institutional, should always be quarantined away from other rabbits for up to 2 weeks post-arrival to ensure that they are free of opportunistic disease.

Public Health Significance

Psoroptes spp. mites of rabbits do not affect humans. *C. parasitovorax* and *Leporacarus* spp. mites, in rare cases, can cause dermatitis in humans, especially children. Both mites may also infest other companion animals such as cats. *N. cati* of rabbits also may cause transient dermatitis in humans. *S. scabiei* is zoonotic and may induce intense pruritus in humans and other companion animals.

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Acariasis in the Guinea Pig

Etiology

The most common species of guinea pig mites is *Chirodiscoides caviae*, a small, generally harmless fur mite, and *Trixacarus caviae*, a burrowing sarcoptid mite. *Trixacarus* spp. may be confused easily with *Sarcoptes* and *Notoedres* spp. Some early reports of the latter mite infections may have been caused by *Trixacarus* spp.

Clinical Signs

T. caviae of guinea pigs frequently produces a severe, dry, scaling, and crusting dermatitis and alopecia on the neck, shoulders, inner thighs, and abdomen, which often results in intense pruritus and self-mutilation, with frantic scratching culminating in seizure-like activity. Maximal parasite load is reached approximately 1 month after infection, then parasite numbers slowly regress if left untreated. Mortality of infected guinea pigs has been reported in rare cases. In contrast, few clinical signs or lesions may be seen with *C. caviae* infestation, even though the parasites may be numerous.

Diagnosis

The pelt can be examined effectively for *C. caviae* mites with a hand lens or a dissecting microscope. The mites concentrate in the lumbar region and lateral aspects of the rear legs. Adult

C. caviae mites can be seen with the unaided eye moving in the fur. *C. caviae* mites are usually seen in pairs, which represent a noncopulatory union of juvenile males with more mature females, presumably to ensure the presence of a mate when both reach sexual maturity.

Lesions of *T. caviae* are typically severe. Mites and ova may be seen histologically in burrows in the stratum corneum or in skin scrapings.

Treatment

Eradication of *C. caviae* infestations has been reported in guinea pigs by spraying dilute (0.2 mg/mL) ivermectin on the coats of infested guinea pigs followed by applying undiluted drops of ivermectin (10 mg/mL) directly onto the coats. A single topical application of selamectin at a dose of 15 mg/kg or repeated SC injection of ivermectin at a dose of 400 µg/kg (four times at 10-day intervals) has also been used to eliminate *T. caviae* mites from guinea pigs.

Ivermectin has been used at 400 µg/kg via oral, SC, and topical routes to treat *T. caviae*. All routes resulted in an effective cure for *T. caviae* when a second dose was given seven days after the first. Ivermectin has also been used SC at 200 µg/kg twice at a 10-day interval to treat guinea pig mange. By 21 days posttreatment, clinical signs had completely resolved. Side effects included subdermal necrosis at the injection site in younger animals and inflammation of the skin in the older animals, possibly due to the propylene glycol used as a diluent. A single topical administration of selamectin at 15 mg/kg was also efficacious in a study in guinea pigs. Similarly, doramectin 1% given twice at 400 µg/kg SC or IM at 7-day intervals was efficacious in controlling *T. caviae* infestations.

Public Health Significance

C. caviae do not affect humans. *T. caviae* may cause urticaria in humans, but infestation is transient and self-limiting.

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Acariasis in the Hamster

Etiology

Several species of mites have been described in hamsters: *Demodex criceti* is found in epidermal pits and *D. aurati* is found in the pilosebaceous glands and hair follicles. *Notoedres* spp., a burrowing mite, can cause scabby lesions of the ears, feet, nose, and genital region. More recently, infestation with the tropical rat mite, *Ornithonyssus bacoti*, has been reported in companion hamsters and their owners. Presumably, these mites were transmitted to hamsters from the pet store of origin or from exposure to feral rodents in the home.

Clinical Signs

A *Demodex* spp. infestation in hamsters is rarely associated with clinical signs, but it may cause alopecia, rough hair coat, and scaly, scabby dermatitis of the rump and back. Demodecosis is particularly common in male hamsters older than 1.5 years and is frequently secondary to chronic renal disease, intercurrent systemic disease, and malnutrition. Pruritus is not a prominent feature of demodecosis of hamsters.

Diagnosis

Demodex spp. is difficult to detect. If *Demodex* infestation is suspected, a deep skin scraping with an oil- or glycerin-wetted scalpel blade will aid in the collection of mites. Scraped material is placed on a slide with a few drops of warmed 10% potassium hydroxide, coverslipped, allowed to sit 10 minutes, and then examined microscopically. Histologically, hair follicles are distorted, dilated, and filled with debris and mites.

Treatment

Demodectic mange and *O. bacoti* infestations in hamsters can be treated with selamectin at a dose rate of 6–18 mg/kg body weight, two treatments of one drop 6% selamectin applied to the skin weekly from a pipette. Ivermectin has also been used with variable effect to treat demodecosis in hamsters. Daily oral treatment with 0.3 mg/kg of ivermectin led to resolution of the infestation in 58% of animals in one study.

Public Health Significance

Demodex mites of hamsters do not affect humans. *O. bacoti*, the tropical rat mite, is zoonotic and can act as a vector to transmit other more serious diseases to humans.

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Acariasis in the Gerbil

Demodex mites occasionally infect gerbils, but demodecosis is not considered a significant clinical disease of healthy gerbils. *Demodex* mites have been seen in skin scrapings from a lesion on the tailhead of a gerbil. The mange described was similar to that seen in hamsters with *Demodex* infections. Avian mite (*Ornithonyssus silviarum* and *Dermanyssus gallinae*) and *O. bacoti* infestations of pet gerbils have been reported with subsequent transmission of mites to their owners. The gerbils were interpreted to be accidental hosts. Mite treatment in gerbils is similar to that described for hamsters.

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Acariasis in the Mouse

Etiology

Mites found commonly on rodents are members of the suborder Prostigmata. Common species of mouse mites include *M. musculi*, *M. musculinus*, and *R. affinis*, all of which are fur mites, and *Psorergates simplex*, a follicular mite that is rarely seen. *O. bacoti* has also been infrequently reported in companion, laboratory, and feeder mice. Morphologically, *Myobia* and *Radfordia* are similar. *Myobia* has one terminal claw on each of the second pair of legs, whereas *Radfordia* has two. *Myocoptes* is a more oval mite with heavily chitinized "boxing gloves" on the third and fourth sets of legs. Mixed populations of *Myobia* and *Myocoptes* are common.

Transmission

Life cycles of all three species are direct with all stages occurring on the host. Hairless (glabrous) mice are therefore not suitable hosts for fur mites. *Myobia* ova hatch in 7–8 days. The egg-to-egg life cycle requires approximately 12–16 days. Typical infections are mixed, although *M. musculinus* is more common in North America.

Predisposing Factors

Black strains of mice are particularly susceptible to chronic hypersensitivity dermatitis that is frequently severe and associated with self-mutilation. In some cases, the pruritic effects of mite infections in these strains are interpreted to initiate self-mutilation. Fur mite infestation has been demonstrated to induce marked IgE production and mast cell degranulation in the skin of various mouse strains, particularly those of a C57BL/6 background. It should also be noted that chronic skin lesions are common in aged mite-free mice of the black strains, so the condition must be worked up carefully in these strains.

Clinical Signs

Typically, even in very heavy infestations, *M. musculi* may cause signs no more dramatic than host scratching. In susceptible mice, hyperactive behavior, excessive scratching, and a roughened hair coat are seen, often with low parasite populations. Alopecia, epidermal scaling, and scant-to-extensive ulceration may occur; however, these signs are likely caused by a scratching response to the allergic or pruritic stimulus induced by the mites (Figure 5.4). The actual number of mites per mouse appears to have little bearing on the severity of the reaction and the extent of the lesions. *M. musculinus* and *R. affinis* may cause similar signs in mice, although they tend to induce less of an allergic response.

Psorergates simplex inhabits hair follicles. As mites and debris accumulate in the skin, follicular invaginations or cysts are visible as small (2 mm) white nodules in the skin of the head, neck, shoulder, and lumbar areas. These nodules are seen best at necropsy on the subcutaneous or underside of the reflected skin.

Diagnosis

More recently, PCR assays of fur or cage swabs or exhaust dust air from the rack plenum filter have been determined to be highly sensitive means of detecting fur mite infections in mice. Recent surveys suggest that non-PCR methods contribute

to significant underestimation of the prevalence of these ectoparasites. Ectoparasites of mice and rats can be seen incidentally at the time of microscopic examination of perianal cellophane tape impressions for pinworm ova (*Syphacia* spp.). Strips of heavy cellophane or clear packing tape can be pressed firmly against the fur of the live animal and examined microscopically for ectoparasites. The dorsal fur tape test is a quick and inexpensive diagnostic procedure to assess the degree of fur mite infection, although a diagnosis can often be made by evaluating hair shafts plucked from the edge of the lesion. Mites are readily observed from skin biopsies and skin sections taken at necropsy. Many systemic effects occur with chronic dermatitis, such as markedly enlarged lymph nodes and spleens, especially in black mice.

Treatment

Rederivation of mouse colonies by cesarean section with cross-fostering onto mite-free dams is an effective means of treating mite infestations.

A "micro-dot" topical skin delivery technique with undiluted ivermectin has been demonstrated to be efficacious for treating mite-infected mice. Two treatments of 2 mg/kg of 1% ivermectin or 10 mg/kg selamectin on the skin between the scapulae are recommended at a 10-day interval (a volume of 5 µL for a 25-g mouse for either agent) to eliminate pinworms and fur mites. Cross-fostering pups from infested dams between 0 and 36 hours after birth and treating weanlings topically with 0.2 mg/kg ivermectin at 9-day intervals was a successful means of eliminating fur mites from a colony of genetically engineered mice that could not be rederived by cesarean section. Ivermectin has been reported to induce behavioral changes and neurotoxicity in some strains of mice. If this is relevant to a colony or an ongoing experiment, the effects should be evaluated on a small number of animals before routinely administering it to different strains of mice.

Large colonies of mice can also be treated with ivermectin in the feed (12 ppm) for 8 weeks.

Moxidectin given to mice orally at 2 mg/kg and repeated at a 15-day interval was effective in eliminating *R. affinis* from a mouse colony with no adverse effects noted. A single dose of 0.5 mg/kg of 0.5% moxidectin pour-on has also been used topically to eliminate *Myocoptes* spp. from mouse colonies. Selamectin may not be as efficacious for long-term elimination of *Myocoptes* spp. infection, when compared with moxidectin in mice.

The effectiveness of different methods of external application of trichlorphon (Neguvon®) and ivermectin was evaluated for treating *M. musculi* and *Myocoptes* spp. infections in conventional laboratory mice as well as feeder colonies of mice. Ivermectin was found to be effective over a longer time period than was trichlorphon. There was no difference in the results obtained with different methods of application. Topical misting over the cages of a 0.1% solution of injectable ivermectin once weekly for 3 consecutive weeks was more practical than individual dipping for large colonies of mice. For mice being bred as feeder rodents for reptiles and raptors, the length of time that ivermectin and trichlorphon persist in the carcass is unknown.

Treatment of both the environment and cages is required for eliminating *O. bacoti* infestations. Synthetic sustained-release pyrethroid sprays can be used for environmental control and may be combined with wall-mounted insect growth regulator disks. In cage resources such as cotton nesting pads or balls or disks of shredded paper strips can be treated with 5 mL of 0.5% permethrin. The treated nesting materials should be replaced at each cage change for up to 8 weeks of treatment. Wild rodents in the facility should be eliminated concurrently to minimize the risk of re-infestation.

Public Health Significance

Psorergates spp., *Myobia* spp., *Radfordia* spp., and *Myocoptes* spp. mites of mice are not known to affect humans. *O. bacoti* can infect humans and transmit several arthropod-borne diseases.

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Acariasis in the Rat

Etiology

Most of the general information presented about clinical signs, diagnosis, and treatment of acariasis in other species of rodents, particularly mice, applies to the rat and is discussed in the earlier sections of this chapter regarding acariasis in other rodent species. Mites commonly found on rats, like those of mice, are members of the suborder Prostigmata. Representative species of rat mites include *Radfordia ensifera*, a surface-dwelling fur mite, and *Notoedres muris*, an infrequently seen burrowing ear mange mite. Rats rarely have *Demodex nanus* infections. *O. bacoti*, the tropical rat mite, also infests domesticated rats. It is not species-specific and is zoonotic. With the exception of *O. bacoti*, the mites described live on the skin surface and obtain nourishment from epithelial debris and tissue secretions. Life cycles are approximately 10–21 days, and ova hatch in approximately eight days, although cycle lengths and intervals vary with host condition and environment.

Transmission

O. bacoti is a blood-sucking parasite that feeds on the host intermittently and most of the time lives off the host in the rodent's nests and bedding. Frequent bedding changes and nest removal preclude the possibility of the tropical rat mite completing its life cycle.

Clinical Signs

Alopecia, epidermal scaling, and superficial epidermal ulceration may occur in cases of mite infestations, but these signs are thought to be caused by a pruritic response to an allergic reaction induced by the mites. Secondary dermatitis caused by *Staphylococcus aureus* colonization may follow self-traumatization. *R. ensifera*, the rat fur mite, may cause clinical signs similar to those caused by mouse mites.

N. muris infestation of the ears of rats may result in a severe proliferative and disfiguring aural dermatitis with intense pruritus most commonly involving the tips of the ears, and also the nose and forelegs.

Nymphal and adult forms of *O. bacoti* intermittently suck blood from the host; the loss of blood may cause anemia, decreased fertility, weakness, and death. As with fur mites, mammalian hosts may develop an allergic dermatitis to burrowing and biting mites, and the pruritic response may be intense.

Diagnosis

A highly sensitive PCR assay is available for detection of *R. ensifera*; otherwise, diagnostic techniques are similar to methods described for other rodents. Engorged *Ornithonyssus* spp. mites moving in the fur can be seen with the unaided eye. Ectoparasites of rats are sometimes seen at the time of microscopic examination of perianal cellophane tape impressions for pinworm ova. Additionally, wide strips of heavy cellophane or clear packing tape can be pressed firmly against the fur of the live animal and examined microscopically for ectoparasites.

Treatment

Treatment is similar to that for acariasis of mice and hamsters with topical application of selamectin or moxidectin. Feral or wild rodents or infected bedding are likely sources of blood-sucking mites in a conventional facility.

Public Health Significance

Radfordia spp. mites of rats do not affect humans. However, *O. bacoti* bites humans and has been demonstrated via experimental studies to serve as a vector for murine typhus, tularemia, Q fever, plague, and other diseases.

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ANOREXIA AND REDUCED FOOD INTAKE

Etiology

Anorexia, a reduction of more than 25% of the daily food intake for three or more days or complete cessation of eating for more than one day, is a common and nonspecific sign in rabbits and rodents. It may arise from a number of underlying conditions including neophobia, lack of access to water, temperature extremes, food changes, an unpalatable or improperly compounded diet, toxin ingestion, gastric stasis, dental malocclusion or oral lacerations, pain, loss of olfaction, obesity, metabolic disorders such as renal failure or vitamin C deficiency in guinea pigs, infectious diseases, neoplasia, loss of cagemates, mechanical factors that prevent access to water and feed, territorial and behavioral traits, for example, a dominant guinea pig hoarding and guarding feed and water supplies, urolithiasis, liver lobe torsion, and other painful conditions. Guinea pigs are especially susceptible to the detrimental effects of short-term anorexia because of their need for exogenous vitamin C, their tendency to develop ketosis when off feed, and their basic behavioral traits. Specifically, sick guinea pigs often appear to lack the will to live, readily go off feed, and sometimes must be gently coaxed into surviving. Guinea pigs are particularly neophobic in their food habits. A change from one food or flavor to another should be done gradually by using transitional mixtures. Young animals should be introduced to new foods that may be used as treats at a later time. This can help to overcome food neophobias seen in all species. It is also important to note that rodents that cannot access water will not eat and can rapidly become compromised. Excessively hard food pellets and inaccessible elevated or nonfunctional sipper tubes or automatic watering devices may result in death, especially in weanlings.

Clinical Signs

Anorexia is a common presenting problem of pet guinea pigs, chinchillas, and rabbits. Clinical manifestations of anorexia are weight loss or failure to gain, absence of feces, abnormal feces, increased susceptibility to disease, enteropathies, dehydration, loss of pups, and death. Irreversible ketosis may develop rapidly in guinea pigs and obese rabbits, even after these animals have resumed eating. It is important to determine if the animal seems hungry and would like to eat, which may be indicative of underlying dental disease, or if it is truly anorexic. The treatment should be adjusted accordingly. Anorexia should be considered a medical emergency in these species because of their small size, stoic natures, and rapid metabolism, and particularly if animals appear distressed or ill, are dehydrated, or in poor body condition. These animals may be in very fragile condition at the time of presentation and may die suddenly if handled roughly. At a minimum, animals should be provided with warmed fluids parenterally, analgesics, supportive enteral feeding, and a comfortable warm place to rest while the assessment of their condition is ongoing.

Diagnosis

Determination of the cause or causes of anorexia is based on history (caging, recent changes, diet, environment, and character of urine and feces); results of a physical examination (oral exam, body temperature, evaluation of the eyes and nostrils, respiratory, and digestive tracts); and on results of a basic work-up including fecal, blood, and microbial examinations, full-body survey and skull radiographs or skull computed tomography (CT), endoscopic-guided dental examination, and abdominal ultrasound examination. Small mammal companions that refuse all food for one or more days are anorectic and because of their high metabolic rate should be treated as a clinical emergency—a "wait-and-see" approach is rarely successful in anorexia cases.

Treatment

Animals with mildly reduced food consumption that are not displaying other signs of illness are often treated successfully by providing free-choice grass hay, rehydrating with a

balanced electrolyte solution (per os, subcutaneously, IP, or IV), and providing a quiet, low-stress environment. Diagnosing and treating the potential causes for the anorexia and functional ileus are paramount in resolving these cases.

Environmental or behavioral problems that result in anorexia may be overcome in the short term by offering small amounts of sweetened or preferred feeds (corn, oats, sunflower seeds, fresh greens and vegetables, alfalfa hay, apples), by changing feeds or feeders and waterers, by giving B vitamins (vitamin B complex at 0.20 mL/kg), or by reducing crowding or separating incompatible or dominant individuals.

Medical causes of anorexia in rabbits and rodents should be treated aggressively. Subcutaneous, intraperitoneal (a more commonly used route in research animals), intravenous, or intraosseous administration of warmed isotonic fluids several times daily will improve hydration and help stabilize the animal. Ideally, the fluid therapy plan should be based on the level of dehydration and the correction of electrolytic and acid–base disorders as diagnosed on the serum chemistry panel and blood gas results. In dehydrated, depressed animals, fluids can be delivered via a sterile 20- to 23-gauge needle into the medullary cavity of the femur. If signs of hypovolemia are present such as hypothermia, low pulse quality, tachycardia or bradycardia, and a slow capillary refill time, more aggressive resuscitation fluid therapy should be given. The vasopressor of choice in rabbits is norepinephrine provided at 0.05–0.2 µg/kg/min, as dopamine failed to show a significant effect on the treatment of hypotension in one study. The prognosis is guarded to poor with signs of hypovolemia.

Syringe-feeding nutritious, high-fiber slurry will help maintain nutritional status, prevent ileus from developing, reverse negative energy balance, and rehydrate the stomach contents. Commercial products are available, for example, Critical Care™, Oxbow® Animal Health (www.oxbowanimalhealth.com).

Anorectic rabbits are often too weak or too ill to eat voluntarily but may tolerate placement of a nasogastric tube made of soft rubber (e.g., 5F pediatric feeding tube). The slurry fed to the rabbit must pass through the diameter of the tube. Because rabbits are herbivores, supplemental diets must be high in fiber, low in fat, and low in carbohydrates, to stimulate the gastrointestinal tract. Most human and carnivore replacement diets are too high in carbohydrates and fat, and too low in fiber to be suitable for replacement feeding of rabbits. A commercial formulation specifically for nasogastric feeding (Critical Care® Herbivore Fine Grind) is available from Oxbow Animal Health. Rabbits with functional ileus may benefit from metoclopramide 0.2–0.5 mg/kg every 6–8 hours PO or SC, provided no obstruction is present. However, metoclopramide treatment as a gastrokinetic is controversial and may not be efficacious in rabbits. If venous access is available, a lidocaine CRI at 30–100 µg/kg/min (see Chapter 3) is an effective motility enhancement drug in rabbits and has also shown to be effective in treating intestinal obstruction. Trimebutine is another gastrointestinal motility regulating drug that is gaining popularity in rabbits, although scientific information is currently lacking on its effectiveness in rabbits. Critically ill guinea pigs should be supplemented with injectable vitamin C at 50–100 mg/animal/day. Analgesics should be administered, because pain may result in anorexia and can be important in the pathophysiology of gastrointestinal stasis. Buprenorphine 0.05–0.1 mg/kg q6-8h SC is the most common analgesic given to these rabbits. If an IV access is available, fentanyl at 2–5 µg/kg/hr is more potent and can be given in combination with lidocaine CRI or ketamine CRI (see Chapter 3).

Once the animal begins eating again, they must be gradually weaned back onto a nutritionally balanced diet. Good-quality grass hay should be available free-choice for rabbits, guinea pigs, and chinchillas. Equine alfalfa cubes and small amounts of fresh fruits and vegetables, such as parsley, celery, carrots, and apples, can also be offered, along with the usual pelleted diet. Human oral caloric replacement products, for example, vanilla-flavored Ensure®, are often readily consumed by rats without prior training, and hamsters willingly accept rice baby cereal from a syringe. Introducing companion and laboratory rodents and rabbits to these supplements before a potentially painful procedure will improve acceptance postoperatively and will facilitate provision of nutritional support.

Esophagostomy and gastrostomy tube placement is described for rabbits; however, these procedures are not commonly used because of the high potential for abscess formation at the site of implantation and poor tolerance of these devices by rabbits. Animals weakened by prolonged anorexia are usually poor surgical candidates.

A thorough dental examination is necessary in all cases of anorexia. Oral ulcers, excess saliva or food in the mouth, and wetting of the ventral cervical area are suggestive of a dental problem. Sharp points due to malocclusion are common on the lateral (buccal) edges of the upper cheek teeth (premolar and molar) and the medial (lingual) edges of the lower cheek teeth. It may be necessary to sedate the animal to conduct a thorough oral examination. In addition to malocclusion, the mouth should also be checked for foreign bodies and tooth root abscesses. Skull radiographs should also be obtained.

If diagnostic work-up suggests an obstruction is present, proximal obstructive cases should be treated with surgery although prognosis is guarded to poor even with surgery. Rabbits with a very large fluid-filled stomach, metabolic alkalosis, and hyperglycemia frequently have a gastric outflow obstruction or are obstructed at the level of the duodenum. More distal obstructions are typically treated medically and prognosis is fair with aggressive medical therapy including lidocaine CRI administration. Gastric dilatation and volvulus are also reported in guinea pigs with a very poor prognosis.

A commonly noted relationship exists between obesity in sedentary rabbits, anorexia, and eventual death. Rarely do rabbits live 3 full weeks after feces no longer appear in the pan. Limited feeding (85–142 g or 3–5 oz/d) of a consistent amount of feed to prevent obesity and overeating or feeding a high-fiber diet to nonpregnant adult rabbits prevents many anorexia problems.

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ASTROVIRUS INFECTIONS

General Comments: Astroviruses are small, nonenveloped RNA viruses first discovered almost 50 years ago, and they are considered an emerging pathogen in both people and animals, although astrovirus infections are thought to be species-specific and it is unclear whether the virus acts as a primary pathogen in causing enteritis in rabbits and other species. In human children, together with rotavirus and norovirus, they are commonly associated with gastroenteritis, although infections are often asymptomatic in adults. The virus infects goblet cells in the small intestine following which it may disrupt the mucus barrier.

Rabbit-specific astrovirus particles are often isolated from meat rabbits exhibiting diarrhea, together with other agents, including rotavirus, coronavirus, and lapine hepatitis E virus, as part of the rabbit enteritis complex (see Enteropathies). Murine astroviruses (MuAstV1 & 2) have been isolated from wild and research mice, and largely asymptomatic infections are widespread in research colonies. The virus may be a contaminant of mouse-derived cell lines used in research settings and may chronically infect some strains of immunodeficient mice. Viral particles can be detected from feces of rabbits and mice; however, PCR assays are not routinely offered by commercial laboratories and may only be available upon special request.

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BORDETELLA BRONCHISEPTICA INFECTIONS

Hosts

Clinical infection with *Bordetella bronchiseptica* is common in guinea pigs, especially after stress. Epizootic respiratory disease caused by *B. bronchiseptica* can result in high mortality in guinea pigs. The bacterium may also be cultured from conventional laboratory guinea pigs as well as from companion animals, with no clinical signs. Outbreaks of *B. bronchiseptica* infection also have been reported in farmed chinchillas in Brazil. Dogs, rabbits, cats, pigs, birds, humans, and other primates may also carry the bacterium and develop clinical infections, but usually *B. bronchiseptica* is an opportunistic pathogen in these species. The hamster seems to be uniquely resistant to intranasal inoculation with *B. bronchiseptica*. Mice and rats, likewise, are not highly susceptible to natural clinical disease but can be infected experimentally with the bacterium and may act as carriers in some situations. *Bordetella hinzii* is noted occasionally as a spontaneous infection-inducing upper respiratory disease in conventionally housed laboratory mice.

In experimental trials, *B. bronchiseptica* caused pneumonia and was more pathogenic for the respiratory system of weanling rats than was *Rodentibacter complex* (previously known as *Pasteurella pneumotropica* or *Rodentibacter heylii*). Young (8- to 10-week-old) specific pathogen-free (SPF) rabbits,

given hydrocortisone to simulate stress, developed similar degrees of pneumonia when inoculated with either *B. bronchiseptica* or *Pasteurella multocida*. *B. bronchiseptica* antibodies are highly prevalent in conventionally reared research rabbits and commercial meat rabbits, and are rarely associated with clinical signs of disease.

Etiology

B. bronchiseptica is a small, motile, Gram-negative bacillus or coccobacillus. After incubation for 48 hours at 37 °C on blood agar, *Bordetella* colonies are approximately 1 mm in diameter, yellowish-brown, and variably hemolytic. The bacterium does not ferment carbohydrates but does split urea.

Transmission

Transmission of *B. bronchiseptica* is by direct contact with clinically affected animals, carrier hosts, contaminated fomites, and respiratory aerosols. Interspecies transmission is likely. Although many surviving animals eventually develop immunity and eliminate the infection, subclinical infections and carrier animals are common, and *B. bronchiseptica* can be cultured from the upper respiratory tract and trachea of clinically normal animals. Uterine infections (metritis) have been reported.

Predisposing Factors

Many outbreaks of *B. bronchiseptica* infection are precipitated by stressors such as nutritional imbalances, climatic and temperature changes, drafts, season (winter), crowding, feed changes, experimental procedures, intercurrent diseases, and marginal diets, especially those deficient in vitamin C, in the case of guinea pigs. Guinea pigs, particularly the young, pregnant, anorectic, ketotic, and aged, are susceptible. Contact with potential carrier species, such as rabbits, dogs, cats, and nonhuman primates, and mixing of guinea pigs from multiple sources should be minimized.

Clinical Signs

Clinical signs of *B. bronchiseptica* infection in guinea pigs are usually associated with pneumonia and vary from no signs to anorexia, inappetence, nasal and ocular discharge, dyspnea, and death. The incubation period is 5–7 days. The acute or epizootic form of the infection has a sudden onset and lasts 2–3 days. High mortality, abortions, and stillbirths are noted in guinea pigs during epizootics, which occur when the agent is introduced into uninfected susceptible colonies. Enzootic infections often follow epizootics. A decrease in immunity of individual animals from enzootically infected colonies may result in isolated cases or waves of clinical disease.

Rabbits frequently harbor *B. bronchiseptica* in their upper respiratory passages, including the paranasal sinuses. The usual consequence, through ciliary and epithelial damage, is a predisposition to other infections, particularly pasteurellosis, although primary *B. bronchiseptica* rhinitis is occasionally noted.

Necropsy Findings

The most common necropsy finding is discrete anteroventral consolidation of one or more lung lobes. The affected lung is firmer than normal and dark red or reddish-tan to gray. Mucopurulent exudate with otitis media, rhinitis, and tracheitis may be seen independently or may accompany bronchopneumonia. The histologic features of epizootic bronchopneumonia that characterize *B. bronchiseptica* infection in guinea pigs are suppuration, exudation, and hemorrhage. Additionally, there may be marked purulent bronchitis. The lumena of the air passageways contain substantial amounts of heterophils, mucus, and desquamated bronchiolar epithelium, which may extend to terminal bronchioles. Alveoli are packed characteristically with degenerating, protein-rich masses composed largely of cellular debris, primarily heterophils, and fibrin. Although rabbits are much less likely to develop overt disease than are guinea pigs, they may have similar lesions when affected.

Diagnosis

A definitive diagnosis is based on clinical signs and culture of *B. bronchiseptica* from exudate of the nasopharynx, trachea, bronchial lumen, or middle ear on 5–10% blood agar, MacConkey agar, or nutrient broth. Slow growth is characteristic and results in small 0.5 mm colonies at 24 hours. The pearl-like, variably hemolytic colonies reach a maximal size of 2–3 mm by 72 hours. When nasal swabs are used to screen animal colonies for carriers, MacConkey agar is the preferred culture medium because it retards growth of contaminants. Frequently, pure cultures of *B. bronchiseptica* can be recovered from the tympanic bullae of animals with suppurative otitis media. Other common causes of bacterial pneumonia in guinea pigs to be considered in the differential diagnosis are *Streptococcus zooepidemicus* and *S. pneumoniae*. Fresh isolates can be used in serodiagnosis with an agglutination test using known immune serum. Otitis media can be detected in living guinea pigs as tympanic membrane cloudiness visible through a pediatric otoscope, and by radiographic examination of the tympanic bullae. An enzyme-linked immunosorbent assay (ELISA) serologic test has been reported to be more effective than culture in detecting guinea pigs infected with *B. bronchiseptica*, but is not widely available from commercial laboratories. Other diagnostic tests include tube agglutination, microagglutination, and indirect immunofluorescence.

Treatment

Treatment of clinical *Bordetella* bronchopneumonia in rabbits and rodents is usually not practical except in individual pets, and even then, treatment of chronic infection is

palliative. Culture and sensitivity of swabs from affected animals is advised. Affected guinea pigs should be force-fed, as needed, and given fluids and ascorbic acid orally or by injection.

A variety of injectable and oral trimethoprim–sulfa products are available for use in guinea pigs, most commonly trimethoprim–sulfamethoxazole (30–50 mg/kg, PO, twice daily). Sulfamethazine in the drinking water at 4.0 mL of a 12.5% stock solution per 500 mL (166–517 mg/L) for 1–2 weeks may suppress, but rarely cures, an active infection. Enrofloxacin (5–10 mg/kg PO twice daily) and marbofloxacin (4 mg/kg/day, PO) often demonstrated good activity against this agent.

A fatal enterocolitis caused by clostridial toxin release after antibiotic therapy may develop in guinea pigs. Narrow-spectrum drugs with activity against anaerobic bacteria that may allow overgrowth of *C. difficile* include penicillin, cephalosporins, lincomycin, clindamycin, and erythromycin. Safer antibiotics for guinea pigs include enrofloxacin, marbofloxacin, trimethoprim–sulfa (sulfadiazine), or various aminoglycosides. Fluoroquinolone antibiotics should be used with caution in immature animals because of their toxic effects on developing cartilage. If diarrhea develops following administration of any antimicrobial, the drug should be withdrawn.

B. bronchiseptica was eliminated from a colony of guinea pigs without treatment through isolation and bacteriologic screening techniques. Embryo transfer and cesarean-section rederivation have been successfully used to eliminate *B. bronchiseptica* infection from guinea pig and rabbit colonies.

Prevention

Good husbandry, purchase of clean stock, and separation of possible carrier animals from healthy guinea pigs are essential. A *Bordetella*-free colony must be managed on the closed-colony principle (no entry of foreign animals allowed) or with entry restricted to guinea pigs from colonies that are known to be free of the organism. Guinea pigs with enzootic *B. bronchiseptica* infections are unsatisfactory for research because they may unexpectedly succumb to infection, particularly when stressed. Rabbits deserve special attention as a source of infection because *B. bronchiseptica* is a potential pathogen. Weanlings may be inapparent carriers of *B. bronchiseptica* and are housed frequently in the same facilities as guinea pigs.

A single IM injection of formalin-killed bacterin with incomplete Freund's adjuvant resulted in protective serologic titers in guinea pigs lasting 4–6 months. Prolonged use of an autogenous bacterin with intermittent sulfamethazine in the drinking water eliminated the carrier state in an affected colony. However, a colony may experience high morbidity and mortality before the bacterin can be developed.

Two IM injections of 0.2 mL of a nonadjuvanted bacterin developed for dogs (Bronchicine, Dellen Labs, Omaha, NE) at 3-week intervals followed by a booster injection every 6 months induced protective immunity against a lethal challenge of virulent *B. bronchiseptica* in strain 13/N guinea pigs. An attenuated bacterin prepared from the heat-sensitive (34 °C) porcine ts-S34 mutant of *B. bronchiseptica* was reported to grow in the guinea pigs' nasal passage but not in the lungs. Protective antibodies were produced after intranasal administration of the bacterin. Commercially available porcine *B. bronchiseptica* bacterins also protected guinea pigs against fatal pneumonias.

Public Health Significance

The importance of *B. bronchiseptica* infection in humans is likely minimal, although the organism is recovered occasionally from the human nasopharynx and could serve as a source of infection to guinea pigs. The organism can cause a whooping cough syndrome and bronchopneumonia in elderly persons. Classical whooping cough in children is caused by the related organism, *B. pertussis*.

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CESTODIASIS (TAPEWORM INFECTION)

Hosts

Cestodes or adult tapeworms and their intermediate forms infect a wide range of species worldwide. These include rabbits, hamsters, rats, mice, and gerbils. Guinea pigs rarely are infected with tapeworms.

Etiology

Hymenolepis nana (R. nana), the dwarf tapeworm, is found in rodents, especially hamsters, and may rarely infect primates, including humans. *Hymenolepis diminuta*, the rat tapeworm, may be found in rats and other rodents. Adults of *Taenia pisiformis* are

found in the intestine of carnivores and the larvae (*Cysticercus pisiformis*) in rabbits. The larval stage of *Taenia taeniaeformis*, *Cysticercus fasciolaris*, occurs in mice and rats. Adult forms inhabit the intestines of cats and other carnivores. The larval stage of *Taenia (Multiceps) serialis, Coenurus serialis*, is found in intermuscular connective tissue of rabbits. The adult stage occurs in the small intestines of dogs and foxes.

Transmission

H. nana has three life cycle variations. In the direct cycle, ova in proglottids are passed in the feces from one definitive host and are ingested by another. The prepatent period is 15–30 days. Tissue migration by the parasites occurs in this cycle, as it does in the second or autoinfection cycle variation in which ova mature in the intestinal lumen of the definitive host without leaving the intestine. In the third or indirect cycle, there is minimal host reaction because tissue migration does not occur; the ova are passed in the feces from a definitive host through an intermediate host, such as beetles, cockroaches, or fleas, to another definitive host following ingestion of the insects.

H. diminuta ova appear in the feces of the definitive host and are ingested by insects. When the insects are eaten, the ova are passed to another definitive host. Because of the requirement for an intermediate insect host, *H. diminuta* infections are rarely noted in contemporary laboratory rodents, although they have been seen in imported genetically engineered mice.

Taenia ova are passed in proglottids in carnivore feces and are ingested by the rabbit or rodent usually during ingestion of feces-contaminated food. Embryos pass from the intestines via hepatic portal veins to the liver and, less often, lungs and mesenteric lymph nodes. Maturation in the liver requires 2–4 weeks, when the larvae leave the liver as cysticerci. The cycle is completed when the carnivore eats the rabbit or rodent.

Predisposing Factors

General debility and absence of previous exposure to cestodes predispose the host to the more serious effects of infection. Contamination of feed and bedding with carnivore and rodent feces contributes to the spread of cestodes to rabbits and rodents. Susceptibility and reaction to cestode infections vary with the host's sex, age, strain of animal, and virulence of the parasite. For example, DBA/2 mice are more susceptible to *Hymenolepis* spp. infections than are C3H mice.

Clinical Signs

Infections with *Rodentolepis* and *Hymenolepis* species are typically subclinical in rodents. Prevalence of infection is common in pet rodents purchased from large distributors in which many rodent species from different breeders are mixed with little separation between species. When present in large numbers, cestode infections may cause catarrhal diarrhea, weight loss, and death.

Taenia infections are, with rare exception, subclinical in rabbits and rodents, but in heavy infections, nonspecific clinical signs including abdominal distention, lethargy, and weight loss may occur. A rabbit with *T. serialis* infection will develop a coenurus (bladder worm and cyst) in subcutaneous connective tissues, fascial and muscular planes, the brain, and within the abdomen. The coenurus forms daughter cysts with scolices that compromise the host further. Clinical signs depend on the extent to which tissues are affected or displaced. Exophthalmos due to intraocular *Taenia serialis* cyst formation has been reported in a pet dwarf rabbit, and exophthalmos caused by an orbital *Taenia* coenurus has been reported in a chinchilla. *T. taeniaeformis*–induced metastatic hepatic sarcoma has also been reported in a pet rat.

Necropsy Signs

Adult worms are found in the small intestine and occasionally in the pancreatic and biliary ducts of rodents. Worm masses migrate into the anterior two-thirds of the small intestine after ingestion of a meal by the host. When the stomach is empty, the worms retreat to the posterior two-thirds of the small intestine.

T. pisiformis cysticerci, containing a single scolex and measuring up to 2 cm in diameter, are found attached to the mesentery and viscera of rabbits. Hepatic lesions resulting from migration of the larvae appear as pale streaks with sharp boundaries beneath the capsule of the liver. They grossly resemble the hepatic lesions of *Eimeria stiedae* infection, but *Eimeria* lesions are usually more concentric with less distinct edges.

There are usually between 1 and 10 *T. taeniaeformis* cysticerci, which appear as white-to-clear, thick-walled cysts in the rodent liver. The cysts, which grossly resemble abscesses, are several millimeters in diameter, contain a coiled strobila, and are nonreactive if undisturbed.

T. serialis cysts contain multiple scolices and are up to 5 cm in diameter. Most often they are found in the subcutis and in connective tissue of skeletal muscle in rabbits, but they may occur in other tissues.

Diagnosis

Hymenoolepis nana is identified by its oval ova (44–62 × 30–55 µm), which contain an embryo with three pairs of small hooks. The adult tapeworms (20–30 mm × 1 mm) occur in the small intestine or pancreatic and biliary ducts and are found at necropsy. Oncospheres (16–25 × 24–30 µm) occur in the lamina propria of intestinal villi. *H. nana* adult forms are approximately the size of a rodent villus in length and may be found interdigitating between villi, whereas *H. diminuta* adults are considerably larger and are found in the intestinal lumen.

H. diminuta adults are 20–60 µm × 4 mm and the ova are 52–81 × 62–88 µm. Because *H. diminuta* ova are not shed individually but reach the environment in proglottids shed in

the feces, flotation techniques to find ova in the feces are not reliable diagnostic tests.

T. pisiformis larvae in rabbits are recognized at necropsy in the liver as scattered white foci on the capsular surface or within the abdominal cavity as cysts with a single scolex. The larval cysts are usually between 0.5 cm and 2.0 cm in diameter. Histologically, the *Taenia* migration lesion in the hepatic parenchyma consists of focal granulomas that contain scattered heterophils. In contrast, *E. stiedae* lesions seen with hepatic coccidiosis in rabbits involve the bile duct epithelium (destruction, hyperplasia, oocyst development) and adjacent portal tissue (fibrosis with chronic inflammatory cell infiltration).

T. serialis larvae may be detected by observation and palpation of cysts, aspiration of cyst fluid, or by demonstration of cysts at necropsy. *T. taeniaeformis* larvae in rodents are detected in the liver at necropsy.

Treatment

Thiabendazole (0.3% in the feed for 7–14 days) or uredofos (25 mg/kg in the drinking water or 125 ppm in the feed for six days) has been used successfully to treat cestode infections in mice. Praziquantel (Droncit®) in the feed at 140 ppm for 1 week eliminated *Rodentolepis* in mice. Mebendazole at 1 g/kg of feed for 14 days killed cysticerci of *T. pisiformis*. This was approximately equivalent to a dose of 50 mg/kg BW per day. *Taenia* infections in rabbits are not treated. *T. serialis* cysts can be removed surgically unless they are too numerous or inaccessible. Treatment should be accompanied by husbandry changes to prevent reinfection.

Prevention

Cestode infections are prevented by excluding carnivores, wild rodents, arthropod vectors, and insects from rabbit and rodent colonies. Food and bedding should be clean, and dogs and cats in the immediate area of rabbits and rodents should be treated for tapeworms. High humidity favors the survival of cestode ova in the environment.

Public Health Significance

Some *Hymenolepis* (*Rodentolepis)* spp. are zoonotic for humans and may cause enteric disease. *T. pisiformis* does not affect humans, but *T. taeniaeformis* may, if the rodent is eaten and is not sufficiently cooked. *T. serialis* larvae can affect humans as they affect other intermediate hosts.

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COCCIDIOSIS (HEPATIC) IN RABBITS

Hosts

Coccidia strains are highly host-specific, and within the host, reside in specific anatomic locations. Hepatic coccidiosis is a protozoal disease of rabbits and wild lagomorphs and was the

first protozoal disease and protozoan identified by Van Leeuwenhoek in 1678.

Etiology

E. stiedae is potentially a highly pathogenic protozoan commonly found in domestic rabbits. Sporulated oocysts excyst in the duodenum and pass via blood and lymph to the liver and other organs. Schizogony and gametogony occur in the biliary epithelium, and unsporulated oocysts pass via bile ducts to the intestine. The prepatent period is 15–18 days.

Transmission

Transmission of *E. stiedae* is by ingestion of sporulated oocysts passed in the feces. Sporulation requires two or more days outside the host, and reinfection is unlikely to occur with coprophagy. Long-lasting immunity develops after initial exposure. Coccidial oocysts are extremely resistant, and viable oocysts may be found in soil, feed, and on personnel, vegetables, caging, and utensils. Oocysts remain infectious in the environment for several months.

Predisposing Factors

Factors predisposing to clinical coccidiosis include lack of immunity to a specific coccidium, number of oocysts ingested, and general disease resistance of the host. Although 3- to 4-week-old rabbits may have oocysts in their feces, the disease is usually more severe clinically in 5- to 8-week-old weanling rabbits, especially those in unsanitary, contaminated environments.

Clinical Signs

Infection with *E. stiedae* is usually subclinical, but consequences in an animal without previous exposure are dependent on the number of oocysts ingested. Anorexia, failure to gain weight, weight loss, a pot-bellied abdomen, icterus, diarrhea, debilitation, and death can occur. In young, susceptible animals exposed to many oocysts, mortality can reach 50% or higher. Hepatic coccidiosis can be expected to alter many liver and serum components and other physiologic functions so that infected rabbits are generally unsuitable for research.

Necropsy

The most common sign of hepatic coccidiosis at necropsy is few-to-numerous, focal-to-coalescing, yellow-white linear tracts or nodules on the liver surface (Figure 5.5). These foci are irregularly shaped, raised, and, when cut, may ooze a yellow-green fluid. The cords are several millimeters in diameter and course into the body of the liver following the path of affected bile ducts. The gallbladder and major extrahepatic ducts also may be thickened, distended, and contain yellow-green fluid. The number of foci and the degree of hepatomegaly are directly related to the number of infective oocysts ingested. The liver is usually enlarged, up to several times normal size, in severe infections. Hepatic fibrosis with inspissated bile in affected ducts may be evident on cutting the liver. Grossly, bile duct hyperplasia may be so extreme as to resemble neoplasia.

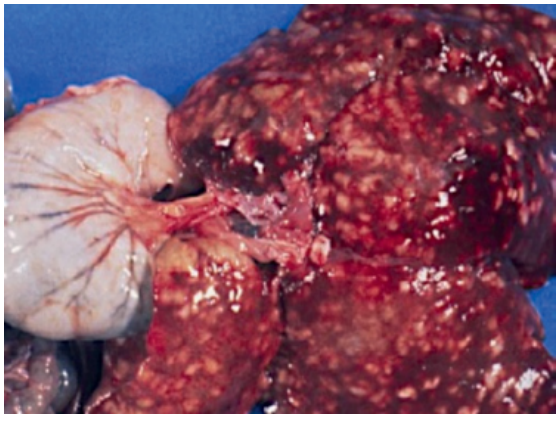


FIGURE 5.5. Liver and gall bladder from a rabbit with severe hepatic coccidiosis due to *Eimeria stiedae* infection.

The microscopic lesion consists primarily of papillary hyperplasia of the biliary epithelium, which usually contains coccidia intracellularly in various stages of development. Occasionally, infection and compression of hepatocytes adjacent to portal areas result in mixed inflammatory cell infiltration and fibrosis. Sometimes enlarged bile ducts will rupture, releasing contents into surrounding tissue, initiating a severe granulomatous response. Histopathologic examination of livers from rabbits recovered from active hepatic coccidiosis demonstrates periportal fibrosis and varying amounts of lymphoplasmacytic infiltration. Remnants of lesions may remain for the life of the rabbit and may confound subsequent pathology interpretation.

Diagnosis

Diagnosis is by recognition of characteristic lesions at necropsy. Flotation and concentration–flotation methods are used to detect oocysts in the feces or bile. *E. stiedae* fecal oocysts are elongated ellipsoidal bodies, about $20 \times 37\ \mu m$ and distinguishable from other oocysts of the rabbit based on size, shape, and structure. Oocytes also may be found in the bile. The oocysts are smooth and light yellow, with a wide thin micropyle and residual body, and the sporocyst has a terminal knob (Stiedae body). Histologically, developmental coccidial stages can be demonstrated in the bile duct epithelium. In heavy primary infections, especially in young rabbits, death may occur before oocysts appear in the feces. Examination of direct smears prepared from cut surfaces of liver lesions at necropsy is an excellent diagnostic technique.

Treatment

Hepatic coccidiosis is best prevented or controlled through rigid sanitation practices. Effective treatment is possible only during a short, inapparent stage early in the asexual part of the protozoan life cycle. For all practical purposes, hepatic coccidiosis, ordinarily a subclinical disease, is untreatable. Treatments used for intestinal coccidiosis may be of value in controlling hepatic coccidiosis; however, robenidine, a commonly used coccidiostat for intestinal coccidiosis in meat rabbits, is not effective against *E. stiedae*. A single oral dose of 2.5–5 mg/kg toltrazuril or ponazuril or a single oral dose of 50 mg/kg sulfadimethoxine followed by continued treatment in the water at 1 g/4 L for nine days has been found to reduce fecal oocyst count in companion rabbits. In commercial meat rabbit production facilities, sulfonamides are typically used as a preventative as toltrazuril is not approved for food producing animals in North America. Note that ionophores that are commonly used to treat coccidiosis in poultry are toxic to rabbits.

Prevention

Prevention of coccidiosis rests primarily with the use of good husbandry and sanitation, that is, clean stock, proper equipment, regular environmental sanitation, and vector control. The use of coccidiostats often results in frustration because of confusion about dosages and regimens and the reappearance of the disease when the drug is removed.

Adult rabbits may be asymptomatic carriers of *Eimeria* spp. This state, combined with the difficulty of eliminating oocysts from caging, bedding, and soil, makes coccidiosis difficult to eliminate from a rabbit colony. Control of coccidiosis requires screening resident and incoming animals for oocysts in the feces, culling infected animals, and strict cleaning and disinfecting procedures. Oocysts are commonly found in the feces of clinically healthy rabbits, and a "clean" pet, breeding doe, or conventionally housed rabbit is rare.

Detergents, disinfectants, and a scrub brush vigorously applied to cages will remove the organic material in which viable oocysts reside, but no commonly used disinfectant, used as directed, kills coccidial oocysts. Hot 2% lye solution, flaming, heat sterilization (e.g., 120 °C for 20 minutes), steam cleaning, and small hazardous molecules as 10% ammonia solution, methylbromide, and carbon disulfide may be used to kill oocysts. Cleaning with and exposure to pressurized hot water and steam are perhaps the most practical methods for eliminating oocysts from an environment. Soil removal, where appropriate, may also be used. The use of sipper tube waterers and hopper feeders is extremely important in preventing coccidiosis, as is elimination of vermin and education of handlers.

Drugs, especially sulfonamides, are used to prevent coccidiosis; however, the only drug product approved for use in rabbits by the US Food and Drug Administration is a specific preparation of sulfaquinoxaline (Sulfaquinoxaline Premix 40%®), which is no longer marketed. Other sulfaquinoxaline products, though unapproved for rabbits, are available. Rabbits so treated should not be slaughtered for food until the required 10-day withdrawal period has passed. The responsibilities for residues remaining at slaughter lie with the owner or prescribing veterinarian. Sulfonamides also have a variety of side effects that can adversely affect medical research. These effects range from inhibition of phagocytosis to nephrotoxicity to blood-clotting disorders.

Rabbit feeds supplemented with 0.025–0.03% sulfaquinoxaline and fed continuously during the critical weaning period (3–8 weeks) are reported to reduce coccidiosis and acute pasteurellosis in young rabbits. Sulfaquinoxaline may also be added to the drinking water at 0.025–0.1%. This drug is given continuously for 4–8 weeks or for alternating "on–off–on" 2-week periods, the intent being to have the drug present at adequate levels when oocysts excyst.

Other prophylactic regimens include daily ingestion of succinyl sulfathiazole (0.625 g), 0.05–1.0% sulfamethazine in the feed, and sulfadimethoxine at 75 mg/kg for seven days. Sulfamethazine (0.2%) and sulfamethoxine (0.5–0.7 g/L) may be administered in the drinking water on a five-day on–off schedule. Toltrazuril (50 ppm in the drinking water) has been used with ivermectin (1 mg/kg SC) to good effect in treating experimental infections of *E. stiedae* in rabbits. These drugs may control the protozoan until the body's defenses overcome the infection.

The most important consideration in controlling coccidiosis is to prevent rabbits from contacting infective feces or contaminated food and water containers by frequent cleaning, use of self-cleaning cages (i.e., elevated floors), and using external feeders and waterers. Coccidiostats may provide a short-term palliative treatment until husbandry and management practices can be revised to control infection of susceptible stock.

Public Health Significance

Eimeria species of rabbits do not affect humans.

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COCCIDIOSIS (INTESTINAL)

Hosts

Intestinal coccidiosis occurs frequently in rabbits, and the protozoa (caused by different species) may occasionally be transmitted from wild rodents, in which they are common, to laboratory or companion rats and mice. Laboratory or companion guinea pigs occasionally have intestinal coccidia.

Etiology

Coccidiosis is the only major enteric protozoal parasitic disease of domestic rabbits. The disease can be caused by concurrent infection with several different *Eimeria* species of varying pathogenicity. Different *Eimeria* species have distinct and sometimes overlapping ecological niches within the intestinal tract, with the result that mixed-species infections are common, particularly in rabbits. Many diarrhea outbreaks attributed to coccidia are in fact caused primarily by other agents, and it is important to ascertain that coccidia are present prior to initiating treatment. Although coccidiosis is generally a sign of poor environmental hygiene, it can occasionally be seen in well-managed rabbits.

In North America, the primary species inducing intestinal coccidiosis in rabbits are *Eimeria magna*, *E. perforans*, *E. media*, and *E. irresidua*. *E. magna* and *E. irresidua* tend to be more pathogenic species. Differentiation of oocysts to definitively speciate coccidia is not useful in planning therapy or prevention unless hepatic coccidiosis is present. In this case, the oocysts of *E. stiedae* are quite distinct from other coccidia, and the diagnosis can be confirmed at necropsy. Prepatent periods among *Eimeria* species range from 2 to 10 days. Sporulation at 20 °C requires 22 hours for *E. perforans* to 70 hours for *E. piriformis*.

Eimeria falciformis is the most common coccidial agent infecting the large intestine of the mouse, while *E. caviae* infects guinea pigs, *E. nieschulzi* affects the rat, and *E. chinchilla* is found in chinchillas. Prepatent periods range from 7 to 10 days for each of these species, indicating that regular hygiene with removal of the feces and changing of bedding will help to eliminate infections before oocysts sporulate. Host immunity develops against each species; however, immunity against one species will not prevent infection by another species later in life.

The transmission, predisposing factors, treatment, prevention, and public health significance of intestinal coccidiosis are similar to those of hepatic coccidiosis, discussed in the previous section of this chapter. Diarrhea associated with intestinal coccidiosis can be treated symptomatically but is often unsuccessful. In addition to being a direct cause of disease in rabbits, coccidia may predispose animals to bacterial enteritis, particularly from clostridial enterotoxemia and colibacillosis.

Clinical Signs

Coccidia frequently reside in the intestine more as innocuous flora than as pathogenic organisms. This characteristic is common in immunocompetent adult animals; however, the introduction of new *Eimeria* species into immunologically naive young or old animals can produce a range of clinical signs depending on susceptibility of host, extent of infection, and strain of the causative organism. New additions to the household or colony should always be quarantined and ascertained to be free of disease before mixing with established animals.

Intestinal coccidiosis in commercial or pet rabbits is most often a subclinical disease associated with growth retardation and reduced feed conversion. In clinically evident diarrheal outbreaks, the course from first signs to death may vary from several hours to months. Most deaths occur after ingestion of large quantities of oocysts of pathogenic species and may be seen in weanlings from 1 to 3 months of age with a peak at 6–8 weeks, although younger and older rabbits may be affected. In an acute infection, deaths may occur without diarrhea, with rapid onset of intermittent or continuous diarrhea, or a few rabbits may be initially affected with prevalence increasing over several days until most are affected or dead. Inappetence, depression, weight loss, watery-to-mucoid feces, sometimes containing blood, subnormal temperature, and polydipsia are common clinical signs. Chronic infections occur as well, in which case pasty brown-to-black diarrhea may continue for weeks or months. Rabbits that survive may be cachectic, grow slowly, have intermittent pasty feces, or develop intussusception.

In rodents, coccidia are generally considered nonpathogenic; however, *E. caviae* infections in guinea pigs may occasionally result in diarrhea and death.

Diagnosis

Diagnosis involves finding characteristic forms of the protozoa on microscopic examination of intestinal scrapings (wet mounts or impression smears) together with histologic lesions or by detecting oocysts in the feces. It may be difficult to determine if oocysts found in feces are associated with primary clinical disease or if they are the product of an incidental, low-grade infection in a resistant host. Oocysts of various *Eimeria* species have distinct morphologic traits. For example, *E. flavescens* has oocysts that are smaller and more ovoid in shape than the yellow, broadly ellipsoidal or ovoidal *E. irresidua* oocysts.

Table 5.1. Coccidiostats commonly used in rabbits.

Drug	Dosage
Sulfaquinoxaline	1 g/L in water; 125–250 ppm in feed for 14–21 d
Sulfamethazine	1–5 g/L in water; 0.5–1% in feed
Sulfadimethoxine	75–100 mg/kg; 0.5–0.7 g/L in water
Sulfamerazine	2 g/L in water for 10 d
Toltrazuril	25 mg/L drinking water; 10 mg/kg PO qd for 3 d, off 3–4 d, treat for 3 d

Necropsy

In rabbits, no gross lesions may be evident, or there may be segmental dilatation of the small intestine with watery or hemorrhagic content, and serosal hyperemia and edema. Mucosal ulceration may proceed from focal desquamation to coalescing ulcers and Peyer's patch enlargement. Petechiation may be evident on the cecal and colonic serosa.

Both asexual and sexual forms of coccidia infect the mucosal epithelium, leading to swelling and eventual rupture of parasitized cells. Loss of mucosal integrity may lead to ulceration, mixed inflammatory cell infiltration, and increased susceptibility to other pathogenic agents.

Treatment

Treatments recommended for hepatic coccidiosis of rabbits can be applied to intestinal coccidiosis. Some of the various coccidiostats that have been used in rabbits are listed in Table 5.1. Treatments should continue for at least five consecutive days and be repeated after five days. Resistance to common commercial coccidiostats is common. As for hepatic coccidiosis, improved hygiene and environmental decontamination (10% ammonia) of caging, food hoppers, sipper tubes, toys, and so forth are critical for successful elimination of the organism. Separation of weanlings from infected and shedding older rabbits may help to break the cycle of infection. Coccidiosis is common in wild rabbits and companion rabbits should not be allowed to contact feces from feral animals.

Guinea pigs and other rodents affected with coccidiosis have been safely and successfully treated with 2% sulfamethazine in the drinking water for 7–10 days.

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CORONAVIRUS INFECTIONS

These enveloped RNA viruses are species-specific and affect a variety of hosts including mice, guinea pigs, ferrets, cats, dogs, pigs, calves, and humans. In general, young animals are selectively affected, and older immunocompetent animals are relatively refractory to infection and clinical disease. Coronavirus strains may be nonspecific in terms of the organ system affected and induce generalized disease, or they may target the gastrointestinal tract, resulting in diarrhea. Increased susceptibility of very young animals to intestinal coronavirus infection is due, in large part, to decreased turnover of intestinal epithelial cells. For example, as mice mature, the rate of enterocyte turnover increases, allowing an enhanced production of new enterocytes to compensate for loss of cells infected by the virus.

Rabbit

Coronavirus infections occur naturally in rabbits and may play a role in some enzootics of diarrheal disease in this species. Carrier animals have been identified. It has been suggested that carriers may be responsible for the persistence of the infection in some rabbitries where there is a high incidence of mortality due to enteritis. Studies evaluating the prevalence of this virus in rabbitries suggest a rate of 3–40%, although the overall prevalence of infection among companion and laboratory rabbits is unknown, because testing for the agent is not routinely conducted. There is no specific treatment for this condition in rabbits beyond supportive nursing care. Secondary bacterial or protozoal infections are common, and the virus may induce myocarditis that progresses to dilated cardiomyopathy in survivors. Affected animals should be kept warm, clean, stress-free, and dry and be provided with good nutrition and fluids, as needed. Attention should be paid to overall hygiene, and animals with diarrhea should be handled after unaffected animals to minimize viral spread between them. There is no commercial serologic test available for this virus. Circumstantial confirmation of infection may be obtained by isolation of viral particles from the feces of young animals with diarrhea.

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Guinea Pig

A coronavirus has been reported in guinea pigs that is antigenically related to other coronaviruses, including rat and human coronaviruses. Viral infection has been associated with diarrhea and wasting in young guinea pigs. Chronic fecal excretion of coronavirus-like particles has been observed in asymptomatic adult guinea pigs. The significance of these findings requires further study, but it is likely that coronavirus infections play a role in some cases of enteritis in guinea pigs, particularly in young animals. The virus is transmitted by fecal–oral contact, reinforcing the need for good environmental hygiene. The prevalence of viral infection among guinea pig populations is unknown, and there is no commercial diagnostic test for this agent. Definitive diagnosis would require isolation of virus particles from the feces of affected guinea pigs.

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Mice

Mice are the hosts for mouse hepatitis virus (MHV), a widespread and highly contagious coronavirus. MHV infection is often subclinical in immunocompetent mice but it can have many effects on the host immune system. It continues to be one of the most prevalent viral infections in rodent colonies around the world.

Etiology

There are many genetically related strains of MHV, and because it is an RNA virus, it is capable of high mutation rates resulting in antigenic drift. Because of varied tissue affinities, antigenic variation, and differential host susceptibilities, the viral strains induce a wide spectrum of disease in mice. Immunity to the virus is strain-specific and short-lived, and colonies in which the virus has been eliminated can readily become reinfected following another exposure. In addition, many genetically modified strains of mice are not fully immunocompetent, and these animals may not be readily able to clear the viral infection. This has given rise to the common misconception that the virus has a latent phase.

Transmission

MHV infection is highly contagious. The virus is disseminated by aerosol, in the feces, and through direct contact. Because of the ubiquitous and highly contagious nature of MHV in wild rodents and resident mouse populations, the infection can be difficult to exclude from contemporary research animal facilities. The virus may survive for a few to several days outside the host in feces and on fomites. Incoming animals and mouse biologic materials should be determined to be free of infection before mixing with the general mouse population. Shared animal equipment should also be thoroughly cleaned between users.

Predisposing Factors

Depending on the virus strain, MHV has tissue tropism for the gastrointestinal tract (enterotropic, which is more common) or has systemic effects (polytropic), and clinical signs are related to the system of primary infection. Polytropic strains often replicate in the nasal epithelium and disseminate to other tissues. A number of stressors may induce overt clinical disease in infected animals, including but not limited to debilitation, neoplasia, immune system suppression or alteration, irradiation, splenectomy, neonatal thymectomy, or infection with other pathogens.

Genotype and other host factors substantially influence the outcome of MHV infections. For example, immunocompetent adults are generally more resistant to clinical disease than are weanlings, and BALB/c mice are more susceptible than SJL mice.

Clinical Signs

Most MHV infections are enzootic and subclinical. Despite this, animals with active infections typically have immune and physiologic perturbations that can alter the outcome of experimental manipulations performed during the acute phase of viral infection. These changes, coupled with the high prevalence of the disease and highly contagious nature of the virus, contribute to the fact that MHV continues to be one of the most commonly encountered and devastating infections of large research colonies.

Susceptible suckling mice, usually between 7 and 13 days of age, can develop a severe, epizootic, diarrheal disease with high mortality or encephalitis with tremors and spasticity. The diarrheic fluid is yellow and sticky and resembles diarrheal disease of rotavirus and reovirus infections of suckling mice. Pups infected with MHV are often acutely sick, dehydrated, and refuse to nurse, resulting in the loss of the characteristic milk spot (milk-containing stomach visible through the skin). In older mice, loss of weight, breeding inefficiency, jaundice, and death may result.

MHV alters lymphocyte differentiation, immunoglobulin responses to sheep red blood cells, phagocytosis, tumor growth, antibody response, interferon production, infection with other agents, and hepatic enzyme activity. Athymic nude and severe combined immunodeficient (SCID) mice typically cannot clear the infection, and these mice develop chronic progressive emaciation or wasting syndrome with an associated persistent infection of the intestinal tract or nasal mucosa.

Necropsy Signs

A prominent lesion with some strains of MHV in immunodeficient adult mice is a multifocal necrotizing hepatitis, characterized by gray or red foci on the liver surface. These foci may contain multinucleated giant cells as well as other components of an acute inflammatory response.

Depending on the strain of enterotropic mouse coronavirus involved, replication may occur at various sites in the small and large intestine, but manifestations and lesions are usually confined to changes in the small intestine. In the small intestine, coronaviruses replicate selectively in the relatively well-differentiated enterocytes lining villi. The loss of these enterocytes results in collapse of villi and subsequent villous fusion and atrophy. Enteritis in suckling mice is typically seen as a flaccid gut distended with gas and yellow fluid. Histopathologic changes consist of villous atrophy, fusion, vacuolation, desquamation, and syncytial cell formation in the absorptive epithelium at the tip of the villi. Secondary bacterial or protozoal overgrowth is common.

Neurotropic strains of the virus disseminate by viremia and the lymphatics and replicate in the endothelium and parenchyma of the brain, where they cause vascular-oriented encephalitis with neuronal chromatolysis and neurodegeneration.

Diagnosis

Clinical history, necropsy, and histopathologic features are helpful in establishing a diagnosis of MHV infection. Multinucleated giant cells in the nasal epithelium, liver, or absorptive epithelium of the small or large intestine are highly indicative, if not pathognomonic, of MHV infection (Figure 5.6). Use of a "Swiss roll" technique greatly facilitates histopathologic examination of the entire gastrointestinal tract. In this technique, the intestine is opened along its length, the feces are removed, the intestine is rerolled along its length usually around a short stick or toothpick, frozen or fixed, and then embedded in paraffin and sectioned.

An ELISA or immunofluorescent antibody (IFA) test is used commonly to detect serum antibodies to MHV infection. PCR may also be used to detect antigen in fecal pellets and mesenteric lymph nodes during the acute phase of infection. Female mice usually have higher titers than do males because they ingest the infected feces of sucklings. Strains of mice vary in their serologic responsiveness to various strains of MHVs. C57BL/6 mice produce a high antibody titer and are a good sentinel strain for MHV infection. DBA/2 mice, on the other hand, are poor responders for antibody production and should not be used to test for MHV if other strains are available. Positive serology should be confirmed by repeat testing, testing of additional animals, or use of a second diagnostic assay. False positive results may occur due to nonspecific color reactions or subclinical infections of mice with rat coronaviruses (RCVs).

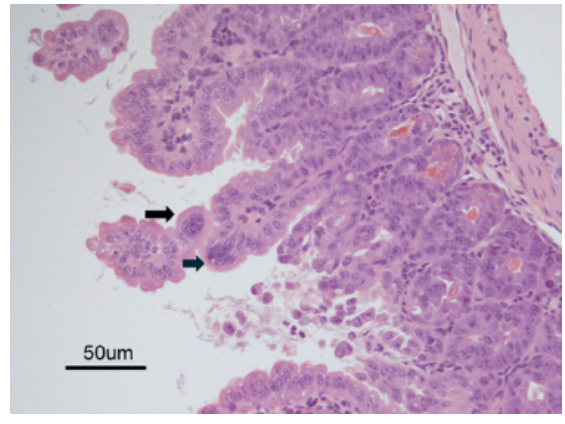


FIGURE 5.6. Section of small intestine from a mouse infected with mouse hepatitis virus (MHV), a coronavirus. Clusters of infected epithelial cells (arrows, syncytia) are being sloughed from the tips of villi, and there are increased numbers of leukocytes within the lamina propria.

Treatment

A satisfactory treatment for MHV infection does not exist. Maternally derived, passive immunity prevented MHV infection in 1-week-old pups that were challenged with a homologous strain of MHV. Pups that were challenged with a heterologous strain were only partially protected.

Because MHV is an RNA virus, it may be possible to eliminate it from an enzootically infected breeding colony of immunocompetent mice by complete cessation of breeding of seropositive animals, without new colony introductions, for an 8-week period, coupled with rigorous environmental decontamination. This is often not practical with large breeding operations, which may more reliably eliminate the virus from colonies by embryo transfer of pups from infected to clean foster dams.

Prevention

Because the source of MHV and other infections is usually other mice, feral or domestic, exclusion of infected animals is paramount to maintaining disease-free populations.

The use of embryo transfer or cesarean-derived mice in a barrier-sustained colony, repeated serologic testing of breeding females, histopathologic examination of dead weanlings, and the use of exclusion filter top cages, gloves, disinfected forceps for handling mice, and laminar flow units are proven preventive measures for minimizing opportunities for MHV spread within a facility. Soiled bedding transfer for sentinel detection of MHV in a colony is not necessarily foolproof, and false negatives may occur, depending on the viral load of infected animals and time of peak viral shedding versus bedding sampling.

Appropriately used, a microisolator caging system provides an effective barrier against MHV infection at the cage level and also protects mice against other infectious agents. Along with use of the microisolator caging system, rigorous sanitary procedures must be practiced. All biologics of animal origin to be administered to mice should be tested via PCR or a mouse antibody production (MAP) test prior to introduction into mice.

Public Health Significance

MHV does not affect humans.

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Rats

Rats are the natural hosts for the highly contagious coronavirus, sialodacryoadenitis virus (SDAV). The self-limiting clinical disease, sialodacryoadenitis (SDA), caused by this agent is seen worldwide, primarily in young rats. Mice may develop a transient interstitial pneumonia with seroconversion.

Etiology

SDAV is a coronavirus (RNA) antigenically related to the MHVs, RCV, and human coronaviruses. SDAV is highly infectious and epitheliotropic and replicates in the cytoplasm, most notably in cells of the respiratory epithelium, and in salivary, lacrimal, and Harderian glands. In contrast, other forms of RCV infection do not generally infect the salivary glands. Infections are common among companion rats and feeder–breeder rat colonies but are uncommon in North American and European laboratory rats.

Transmission

Passage among exposed rats is exceptionally rapid by aerosol or direct contact with respiratory secretions. The respiratory tract is the primary portal of entry. Infected animals secrete the virus for approximately seven days. The disease can be enzootic, but like MHV, SDAV does not exist in a latent carrier state in immunocompetent animals. Mortality is usually low but morbidity and subclinical infection commonly reach 100%. Extension of the infection from the respiratory epithelium is via ducts of the salivary, lacrimal, and Harderian glands. The virus has not been detected in feces.

Athymic rats carry and can transmit the infection for 6 months or longer after inoculation. Prior infection of immunocompetent rats with SDAV protect them against development of typical salivary gland lesions after reinoculation with SDAV for up to 15 months after infection. Immunocompetent rats reinfected with homologous RCV will transmit virus to naive contacts as early as 6 months after initial infection.

Predisposing Factors

Healthy, naive rats of both sexes and all ages are susceptible to SDAV infection, although the severity and site of the lesions vary among hosts of different ages and strains. Susceptible,

young animals, 2–4 weeks of age and with no maternal antibody, develop more serious forms of the disease with the highest mortality.

Clinical Signs

SDA is a highly infectious enzootic or epizootic disease of rats. Whereas clinical signs are seen in a colony for several weeks during an epizootic, individual animals show signs for up to a week. Signs include squinting, photophobia, blinking, and eye rubbing followed by sneezing and cervical swelling within 5–7 days postinfection. Sneezing is associated with acute rhinitis. Swelling under the neck is caused by cervical edema, enlarged cervical lymph nodes, and necrotic and inflamed salivary glands. Bilateral or unilateral suborbital or periorbital swelling, prominent or bulging eyes, and often chromodacryorrhea ("red tears") and ophthalmic lesions develop secondary-to-decreased lacrimation; self-mutilation may occur as a result of scratching the eyes and other affected areas. Very young animals may enucleate the eyeball.

During the infection rats usually remain active and continue to eat, although certain behavioral activities may be suppressed, for example, pain may reduce food intake and complicate feeding studies.

Pneumotropic strains of RCVs may cause an interstitial pneumonia in young rats, particularly of the Fischer 344 strain. This infection may be exacerbated fatally by concomitant Sendai virus infection or mycoplasmosis. There may be high mortality associated with general anesthesia during the pneumonic phase of the disease.

Necropsy Signs

The infection progresses rapidly from the respiratory epithelium to the lacrimal and serous or serous–mucous mixed salivary glands, associated lymph nodes, and contiguous tissues. Affected glands are enlarged, edematous, pale, and often reddened. The thymus becomes atrophic; however, this sign and the chromodacryorrhea may be stress responses. The salivary, Harderian, and exorbital lacrimal glands may all be affected as a group or individually. Lesions are frequently unilateral, and paired salivary and lacrimal glands should be harvested for histopathologic examination.

The glands will return to normal or become permanently scarred, depending upon the severity of the infection and the degree of tissue damage, within 2–4 weeks of infection. Ophthalmic lesions are frequently associated with loss of tears, self-trauma, and inflammation, and range from keratitis sicca to multiple inflammatory sites on and around the eye to corneal ulceration to enucleation.

Immunofluorescent studies demonstrate viral antigen in the respiratory epithelium, lacrimal and salivary glands, and lymph nodes. Epithelial cells of the respiratory tract and ducts and acini of the salivary, lacrimal, and Harderian glands undergo severe necrosis and inflammation. As the virus is eliminated from the lesion in about a week, the restoration process ensues. Provided the basement membranes are intact, tissues will regenerate with minimal permanent scarring. The ductal epithelium undergoes transient squamous metaplasia, and acinar repair is characterized by regenerative hyperplasia. Harderian glands may also have prominent squamous metaplasia. Accompanying changes include persistent mixed inflammatory cell infiltration of the interstitium, tubular blockage, secondary cystic and metaplastic changes, and hyperplasia of local lymph nodes. Athymic rats develop chronic, active lesions that persist in target organs for months.

Diagnosis

MHV antigens cross-react with SDAV antibody in the serum and are often used in ELISA tests. Diagnosis of SDAV is based on clinical signs, histologic lesions, and the detection of serum antibodies. Harderian gland lesions caused by damage associated with blood collection from the retroorbital sinus can be confused with lesions of SDAV infection. Conjunctivitis from other causes may mimic secondary signs of an SDAV infection. Rats without antibody titers to MHV or RCV antigens can be assumed to be free of SDAV antibodies. Virus neutralization, IFA, and immunohistochemical tests may also be useful. Acute infections may be detected by PCR of salivary or Harderian gland tissue.

Treatment

Nursing support by providing the animal with a warm, comfortable environment, tasty food treats, sterile ophthalmic lubricant, and fluids will help to make the pet rat more comfortable during the course of disease, which will last approximately 1–3 weeks. Treatment with antibiotics during the rapid course of the disease can alleviate the effects of secondary ophthalmic trauma and bacterial infections from agents such as *R. heylii*, *Actinobacillus* spp., and *S. aureus*. Laboratory rats are rarely treated because of the potential risk associated with keeping infected animals in a facility and are humanely culled.

Prevention

Susceptible colonies can be isolated and quarantined, but the virus is highly infectious and strict isolation and microisolator caging are usually required to prevent an outbreak from infecting an entire facility. Except in cases of severe keratitis or when eye enucleation is required, the disease usually produces no long-term disability. Immunocompetent rats will clear the infection after exposure to SDAV but may become reinfected with new strains subsequently, as there is little interstrain cross-protectivity.

Public Health Significance

There are no reports of human susceptibility to SDAV.

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CORYNEBACTERIUM KUTSCHERI INFECTIONS

Hosts

Mice and rats are the primary laboratory species affected by *Corynebacterium kutscheri*. Isolation has been reported in the hamster and guinea pig, particularly in cases of bacterial cystitis.

Etiology

C. kutscheri is a small Gram-positive, nonmotile, diphtheroid bacillus that causes corynebacteriosis or pseudotuberculosis. After 48 hours of aerobic incubation on 5% blood agar, colonies are circular, 1–4 mm in diameter, translucent, gray to yellow, smooth, and nonhemolytic. The agent is rare in closed laboratory animal colonies, but infections are common in companion and feeder–breeder animals.

Transmission

C. kutscheri is carried in the oral cavity, colon, rectum, and submaxillary lymph nodes, and transmission is by the oral–fecal route. Prenatal transmission has been demonstrated experimentally. Infected animals may shed the bacterium into the environment for extended periods of time. For example, the organism has been detected in the feces of mice up to 5 months postinfection. *Corynebacterium* spp. have also been isolated from the conjunctiva of normal, apparently healthy rabbits and guinea pigs. Companion rodents, and rats in particular, may transmit the bacterium to their human handlers.

Predisposing Factors

C. kutscheri is considered an opportunistic pathogen in immunocompetent animals. Infections in mice and rats are typically inapparent and become overt after immunosuppression or other stressful manipulations. Nutritional deficiencies, concomitant infections (e.g., salmonellosis or mousepox), corticosterone administration to induce immunosuppression, pregnancy, irradiation, inadequate hygiene, and possibly anemia are predisposing stressors. Rats infected with SDAV, Sendai virus, or parvovirus do not convert preexisting subclinical *C. kutscheri* infections into clinically apparent diseases. Susceptibility to the bacterium varies among inbred strains of mice. Strain A mice, for example, are highly susceptible. Strains of mice sensitive to *C. kutscheri* infection tend to be resistant to *Salmonella* spp. infections and vice versa. Rats are more resistant to acute spontaneous pseudotuberculosis than are mice.

Clinical Signs

The infection is usually latent and subclinical. The acute clinical disease, with high morbidity and low variable mortality (2–10%), is characterized by a rough hair coat, emaciation, rapid respiration, hunched posture, abnormal gait, nasal and ocular discharge, septic swollen joints, and lethargy. In cutaneous infections, the skin is abscessed, ulcerated, and underlaid by fistulous tracts. Loss of necrotic extremities mimics clinical signs associated with mousepox in mice. Death usually occurs within a week. A chronic infection, with low morbidity and mortality, may be inapparent or produce nonspecific signs. This bacterium is also a common isolate in bacterial cystitis in guinea pigs and may lead to urinary signs such as hematuria and abdominal pain.

Necropsy Signs

Hematogenous extension of the organism from the oral cavity via small abrasions or from regional lymph nodes results in focal embolic abscessation in a variety of organs, most notably the kidneys, lungs, heart, mesentery, and liver. The brain, middle ear, lymphatic system, joints, and skin may also be affected. The lesions are scattered, gray to light yellow, and raised with caseopurulent foci up to 15 mm in diameter. There are usually no splenic lesions as in salmonellosis and mousepox. Rats may develop a severe pneumonia with a striking target-like pattern caused by multifocal abscesses against the dark red parenchyma of the lung. The central necrotic portion of each lesion often has an umbilicated appearance.

Histologically, the lesions are chronic and consist of a pyogranulomatous infiltrate around the central necrotic core, surrounded by a mantle of infiltrating lymphocytes, plasma cells, and fibroblasts. Abundant clumps of the Gram-positive

bacteria are evident on smear preparations and in tissue sections. Lung lesions eventually become granulomatous, hence the reason for calling the disease pseudotuberculosis.

Diagnosis

Examination of Giemsa-, Gram-, and silver-stained impression smears from affected tissues or tissue sections often reveals bacteria surrounding the areas of necrotic debris typically arranged in characteristic "Chinese character" patterns and consisting of Gram-positive short, plump rods. Definitive diagnosis requires characterization of bacteria cultured on blood agar or serologic testing. The isolation rate of *C. kutscheri* is highest in specimens collected from the oral cavities and the submaxillary lymph nodes. The organism can also be recovered from the cecum and conjunctiva. Cortisone acetate or cyclophosphamide can be used to trigger latent infections with subsequent culture in diagnostic screening of rat and mouse colonies. The agent is difficult to recover from animals latently infected in enzootically affected colonies, although oral swabs of the gingiva may be helpful. ELISA and DNA hybridization assays can also be used to detect evidence of infection.

Treatment

The bacterium is sensitive to a variety of antibiotics, including ampicillin, tetracycline, and fluoroquinolones. Antibiotic therapy does not eliminate infection but may suppress clinical disease. When treatments are withdrawn, overt disease may resume.

Prevention

Prevention of a *C. kutscheri* outbreak involves selection of clean stock and use of good husbandry practices that take into consideration the fact that *C. kutscheri* survives in the environment. Latently infected carrier animals may be difficult to detect and may be culture-negative. Immunologically compromised mice and rats should be isolated and carefully observed for signs of the disease.

Public Health Significance

C. kutscheri is primarily a rodent pathogen, but a case of chorioamnionitis has been reported in humans and abscessation has been reported in human handlers following a bite from a subclinically infected rat.

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CRYPTOSPORIDIOSIS

Hosts

Cryptosporidiosis may be an important cause of enterocolitis and diarrhea in guinea pigs, chinchillas, rats, mice, nonhuman primates, young ruminants (calves and lambs), foals, snakes, birds, and humans. Asymptomatic infections have been reported in hamsters and rabbits.

Etiology

Cryptosporidium spp. was identified first by Tyzzer in 1907 in the pyloric glands of laboratory mice. Protozoa of the genus *Cryptosporidium* are small (3–6 µm), intracellular, coccidian parasites that typically infect the absorptive surface of epithelial cells covering intestinal villi. Less often, epithelial cells of the respiratory and biliary mucosa may be infected. During infection, cryptosporidia fuse with host membranes, invaginate between microvilli, and ultimately lie within the apex of absorptive epithelial cells or, on occasion, within the cytoplasm of M cells in Peyer's patches. Cryptosporidia produce sporulated infective oocysts. Like other enteric coccidia, only one host is required to complete the life cycle (monoxenous).

Originally, cryptosporidia were considered highly host-specific, as are most coccidia, and each new species was named or speciated based on the host species from which it was recovered. More recent experimental and naturally occurring cross-species transmissions among mammals indicate that *Cryptosporidium* spp. is not a host-specific parasite. The parasite has received increasing attention in recent years because of the potential public health significance.

Transmission

Transmission of cryptosporidia occurs with ingestion of mature and infective sporulated oocysts. Oocysts in the feces of animals with cryptosporidiosis are infective immediately

for other animals. Indirect transmission may occur through contact with oocyst-contaminated food, water, or fomites. Excystation is believed to occur by digestion of the oocyst wall in the gastrointestinal tract of the host. The organism can exist in a latent form for months outside the host.

Predisposing Factors

In immunocompetent hosts, cryptosporidiosis usually occurs as a transient bout of diarrhea with low mortality, but chronic infections may occur in young animals. In immunocompromised or immunodeficient animals, persistent and recurrent infections frequently occur. Recently weaned animals, particularly guinea pigs, are most likely to show clinical signs. Stress caused by shipping and overcrowding may contribute to the severity of disease. Heavily contaminated environments may increase intestinal microbial load and exacerbate clinical signs.

Clinical Signs

Cryptosporidial infections are frequently subclinical and asymptomatic. Lethargy, rough hair coat, failure to gain or maintain weight, and weight loss have all been reported in natural and experimental infections in mice, rats, and rabbits. In guinea pigs, failure to gain weight, watery diarrhea, and occasionally death have been associated with cryptosporidiosis.

Necropsy Signs

There are typically no gross lesions associated with subclinical cryptosporidiosis in rabbits and rodents. Guinea pigs with clinical signs may show emaciation, hyperemia of the small intestine, serosal edema of the cecal wall, and watery content throughout the intestines.

Microscopic examination of affected areas of the intestine in acute cases may demonstrate sloughing of enterocytes at the tips of villi, edema of the lamina propria, and hyperplasia of the crypt epithelium. Villous atrophy, fusion, and hyperplasia may be seen, depending upon the stage of infection, and lymphocytic infiltration in the lamina propria is observed in chronic cases. In Giemsa-stained sections, the organisms may be visualized along the microvillous border of enterocytes. In immunodeficient mice, the ability of the organism to colonize the intestinal tract depends on the makeup of the resident intestinal microflora. In a comparison of susceptibility to *C. parvum*, infections were delayed in mice with intestinal flora compared with germ-free mice. Colonization of the biliary system with cryptosporidia has been observed in immunodeficient mice.

Diagnosis

Diagnosis is made by recognition of clinical signs, characteristic lesions such as parasites in microscopic sections, or by identification of oocysts in the feces. Cryptosporidial oocysts are overlooked frequently in fecal sample analysis because of their small size (7×5 µm) and their morphologic similarity to yeast. Diagnosis of cryptosporidiosis may be facilitated by concentration techniques, such as oocyst flotation from fecal specimens and subsequent examination of meniscal fluid by light or phase-contrast microscopy. Examination of fresh or formalin-fixed fecal smears stained with acid-fast or Giemsa stains may aid in the detection of oocysts. Phase-contrast examination of impressions or scrapings of the ileal mucosa made at necropsy will also reveal the small, mature, birefringent oocysts.

Treatment

Treatments effective for other coccidial species appear to be ineffective for *Cryptosporidium* spp. Supportive care, such as provision of warmth and fluids, should be provided.

Prevention

Prevention of transmission of cryptosporidia is based on the use of husbandry and sanitation procedures that preclude exposure to carrier animals and contaminated objects. Many animal species, especially lambs and calves, may be carriers and sources of infection. Contact between these species or their feces and rabbit or rodent species can result in infection. Oocysts in the environment may be destroyed by treatment with 5% ammonia solution followed by thorough drying or exposure to temperatures below 0 °C or above 65 °C.

Public Health Significance

Because of their infectious nature and tendency to cross species lines, *Cryptosporidium* spp. is a potential public health hazard. Infant mice and guinea pigs may be infected with *C. parvum*, the human cryptosporidial species, and feral rats and mice may be carriers of this agent. Caution is warranted in the handling of potentially infected animals, specimens, and material from the suspected carrier's environment and as always, thorough hand-washing procedures should be used after handling any wild, companion, or laboratory animals. Cryptosporidial infections have been documented in veterinary students and animal handlers who care for young animals with clinical cases of cryptosporidiosis.

The course of cryptosporidiosis in humans is determined largely by the host's immune status. Infection may be asymptomatic or cause profuse, watery diarrhea, abdominal pain, and anorexia. Diarrhea is self-limiting in immunocompetent people, whereas immunocompromised individuals develop chronic, severe diarrhea, which may contribute to the death of the patient. Cryptosporidia cause severe, irreversible diarrhea in human patients with immunologic disorders, especially acquired immune deficiency syndrome (AIDS).

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DERMATOPHYTOSIS (RINGWORM)

Hosts

Dermatophytes are fungal pathogens that use keratin as a nutrient source and affect a range of animals. Most reports of ringworm or dermatophytosis in small mammals refer to rabbits and guinea pigs, although chinchillas, hamsters, and other small rodent species may be subclinically infected, with reported prevalence rates of 5–30%.

Etiology

Trichophyton mentagrophytes is the organism typically encountered in rabbit and rodent dermatophytoses. Several cultural variants of *T. mentagrophytes* exist, a circumstance that leads to confusion in the literature and in the diagnostic laboratory. *Microsporum canis* is infrequently isolated from rabbits and rodents and is thought to be acquired from other domestic animals, such as dogs and cats.

Transmission

Although clinical infections are uncommon, asymptomatic carriers of the dermatophyte are common, and they pose a continuing threat to other animals and caregivers. Dermatophytes are readily transmitted by direct contact with spores on hair coats, in bedding, on grooming equipment, and elsewhere within the environment.

Predisposing Factors

Husbandry and nutritional, environmental, and experimental stress are all potential factors that increase exposure or reduce resistance, predisposing animals to dermatophytoses. Genetic background, overcrowding, inappropriate heat and humidity, ectoparasitism, age, and pregnancy have also been implicated as predisposing factors.

Clinical Signs

Most animals that carry *T. mentagrophytes* have few or no clinical signs of infection. Lesions in guinea pigs usually arise on the face and spread over the back and limbs. Lesions are oval to patchy, hairless and scaling, with crusts or scabs over raised areas. Hamsters present with similar signs. Pruritus, if present, is usually mild. In chinchillas, lesions appear on the nose, behind the ears, or on the front feet, and may spread to any part of the body (Figure 5.7). Lesions on the rat tend to occur over the back, whereas tail lesions may be seen in mice. Scant-to-complete focal hair loss, erythema, scaling skin, and scabs are signs of ringworm infection in mice.

Characteristically, in young rabbits, lesions are more generalized than focal, but there may be 2–3 cm hairless areas with reddening and slight-to-heavy crust formations over the snout, face, forelimbs, or ears. Fur loss on the footpads and toes of rabbits may be due to a progressive mycotic pododermatitis condition wherein treatment is most effective during the early stages. Rabbits may chew their feet and exacerbate the clinical condition.

Diagnosis

The diagnosis may be established by microscopic examination of skin scrapings or plucked hairs taken from the periphery of the lesion and mounted in 10% KOH under a petrolatum-ringed coverslip. Scrapings should be inoculated onto a suitable agar



FIGURE 5.7. Dermatophytosis (circular patch of alopecia) in a chinchilla, caused by infection with *Trichophyton mentagrophytes*.

culture medium and cultivated aerobically at room temperature for at least 10 days. Dermatophyte test medium (DTM) with color indicators is commonly used for culture (growth of saphrophytic fungi does not result in colorimetric change of the medium). Specimens for routine culture screenings can be collected by using a sterile toothbrush or surgical scrub brush to dislodge hair and cellular debris directly onto the agar surface, or the brush with scrapings can be inoculated onto the agar. Histologic sections stained with periodic acid Schiff (PAS) or methenamine silver will aid in confirming a diagnosis. Ultraviolet fluorescence (i.e., use of a Wood's lamp) is only diagnostic for some forms of *M. canis*.

Treatment

Successful treatment of ringworm involves elimination of the organism, not just the lesions. Treatment should be undertaken only after consideration of the public health significance of the fungus.

Topical and systemic antifungal agents are available. Topical antifungal shampoos, creams or lotions, such as those containing clotrimazole, miconazole, or terbinafine, can be applied sparingly twice daily to affected areas of animals for 2–4 weeks. Fluconazole at 16 mg/kg/day has been used with great success in guinea pigs. Dipping the affected toes in an iodine solution several times daily for weeks may be necessary to destroy infective fungus in nail beds. Treatment should be continued until the skin heals and hair regrows.

For chinchillas, a teaspoon of nontoxic antifungal powder (e.g., athlete's foot powder) can be mixed with one cup of dust for bathing. Dust from an infected animal should never be used for a healthy chinchilla.

It is important that the environment be effectively sanitized to eliminate fungal spores. Hair and skin dust should be vacuumed and surfaces wiped with dilute bleach or chlorhexidine wipes. Any towels or bedding used for animal grooming should be washed in hot water with bleach.

Prevention

Maintenance of high husbandry standards is a protective measure particularly with young, aged, pregnant, or recently arrived animals. Culture screening for dermatophytes, optimal adjustment of temperature and humidity, removal of ectoparasites, culling carriers, and sterilization of contaminated equipment are other preventive measures. Hypochlorite (bleach), benzalkonium chloride, and glutaraldehyde are all effective in the environmental control of ringworm in small animals.

Public Health Significance

T. mentagrophytes may infect animal caregivers before it is observed on the animals. The fungus is infectious for humans, particularly very young or infirm persons. Animal caregivers should always wash their hands carefully before handling animals in other rooms, wear gloves while cleaning and treating affected animals, and grooming equipment and dust baths should never be shared between rooms or species without disinfection in between.

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ENCEPHALITOZOONOSIS

Hosts

Among small mammals, rabbits are the principal animal infected by encephalitozoonosis, although guinea pigs and other rodents may be subclinically infected. The disease is common in rabbits, and the infection frequently complicates research and may present as sudden death in companion rabbits.

Etiology

The disease is caused by infection with *Encephalitozoon cuniculi*, an obligate, intracellular, spore-forming, Gram-positive, microsporidian parasite.

Transmission

Ingestion of spores from infected urine is the usual route of transmission between rabbits and within rodent colonies. The major exchange of spores occurs between the doe and her young between the fourth and sixth weeks of life. The young seroconvert during the seventh to ninth week of life. The organism

enters the intestine, passes via phagocytes to the bloodstream, and is distributed to other organs. Spores appear in the kidneys approximately 35 days postinfection. Transplacental and respiratory transmission has also been described for guinea pigs and rabbits.

Predisposing Factors

As with other host–parasite interactions, the severity of infection depends on host resistance and infective dose. Young rabbits and other susceptible species, in which maternal antibodies subside at approximately 4 weeks, are at an increased risk to develop clinical disease if they are housed in unsanitary conditions and eat or drink from crocks that are contaminated with spore-containing urine from infected dams. Prevalence within guinea pig colonies depends on husbandry conditions. Guinea pigs housed with infected rabbits are at greater risk of becoming infected than if rabbits are housed separately.

Clinical Signs

Most cases of encephalitozoonosis are chronic and subclinical and are usually diagnosed on postmortem examination. Less commonly, poor growth, tremors, torticollis, paresis, convulsions, and death may occur weeks after ingestion of infective spores. In a study examining seroprevalence of *Encephalitozoon* in companion rabbits, of animals showing clinical signs, 75% showed neurological signs, 14.6% demonstrated phacoclastic uveitis (Figure 5.8), and 3.5% suffered from renal failure (Figure 5.8), while 6.9% of the animals had combined signs. Vestibular disease dominated within the rabbits that showed neurological signs. *E. cuniculi* infections in mice depress host immunity early in the course of infection.

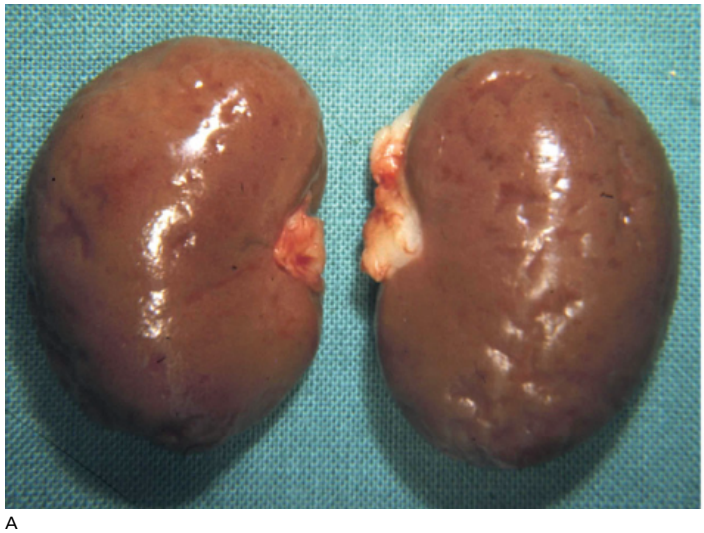
Necropsy Signs

Encephalitozoon has a predilection for the kidney and later the eye and brain, although the lungs, heart, and liver may be transiently affected during the first few weeks after ingestion. The infection is terminated after between 40 and 70 days in the kidney, by which time lesions may be forming in the brain.

In the more acute stages of the disease, the kidneys may be enlarged with grossly apparent small white foci within the cortex. Chronic renal infection is evidenced by numerous, randomly scattered, small (1–3 mm) pits on the cortical surface. The granulomatous brain lesions and renal pitting, caused by tissue destruction and scarring, remain for the life of the animal. Cerebral lesions are not evident grossly, although uveitis may sometimes be seen in dwarf rabbits infected with *E. cuniculi.*

Diagnosis

In rabbits with neurologic signs, positive IgG antibody titers diagnosed with IFAT, ELISA, or CIA assays can help to confirm the disease, although seropositivity does not necessarily indicate that *E. cuniculi* is causative, as many seropositive individuals exist with no signs. Positive IgM antibody titers are typically associated with a more acute infection. PCR testing of kidney tissue or urine is diagnostic, but tests are currently not commercially available. CT scans or MRI may assist with diagnosis of multifocal cerebral lesions characteristic of the disease or for ruling out other important differential conditions, such as otitis media. There is no correlation between



A



B

FIGURE 5.8. Chronic renal disease with pitting of the cortical surfaces (A) may occur in rabbits infected with *Encephalitozoon cuniculi.* Phacoclastic uveitis (B) is only reported in infected dwarf rabbits.

serum antibody titer and severity of clinical disease, and antibodies may persist for greater than 1 year postinfection.

Within the kidney, microscopic lesions include interstitial granulomatous nephritis. Frequently, organisms are seen to be encysted and quiescent in the brains of infected rabbits with no other signs of host reactivity. More active lesions are evidenced by pyogranulomatous inflammation and necrosis within the cerebral parenchyma with lymphoplasmacytic perivascular cuffing. In paraffin-embedded sections, organisms may be identified with Gram (positive), Giemsa, or carbol fuschin stains, in which they appear as oval or crescent-shaped trophozoites approximately 1 µm in length or as pseudocysts 8–12 µm in diameter.

In most cases, histopathologic findings, coupled with serologic or PCR testing, remain the preferred method of diagnostic monitoring for *Encephalitozoon* infections. Pathologists should be aware of the potential for residual lesions of encephalitozoonosis, which can contribute to background effects in the brain and kidney of rabbits and guinea pigs.

Treatment

No effective treatment exists for encephalitozoonosis and some clinical signs may be irreversible. Infected laboratory rabbits are generally culled. Animals with acute episodes of vestibular disease may recover well without treatment. In one study, almost 50% of seropositive rabbits demonstrating neurologic signs, such as head tilt and circling, spontaneously resolved between 2 and 4 weeks later.

Treatment is three-pronged and aimed at elimination of the parasite, reduction of inflammation, and treatment of other associated signs. No currently marketed drugs have label efficacy for *E. cuniculi*. Albendazole (20–25 mg/kg for up to 30 days), fenbendazole (20 mg/kg for at least 28 days), and oxytetracycline have been reported to be efficacious, with claims of fenbendazole eliminating infection, while human HIV patients infected with *E. cuniculi* take fenbendazole for life. Fenbendazole has also been associated with bone marrow toxicity in rabbits and blood cell counts should be monitored during treatment. Diazepam (1–2 mg/kg SC or IV) and prochlorperazine (0.2–0.5 mg/kg PO up to three times daily) can be used to treat acute seizures and vertigo, respectively. Nonspecific supportive care should be given to animals with general signs of renal failure, such as providing warmth, fluids, and a comfortable, quiet area to rest. Lens removal is curative for rabbits demonstrating *Encephalitozoon*-induced phacoclastic uveitis.

Elimination of an infection from an existing colony is difficult, and *E. cuniculi*–positive rabbits will sometimes be found from reputable commercial vendors. Extensive serologic testing and culling of seropositive animals should be used along with good sanitary procedures using disinfectants and hot water to reduce or eliminate infective spores from the environment. Spores may remain viable for 4 weeks or more in dry conditions.

Prevention

Selection of rabbits free of *E. cuniculi* is the best means of preventing colony infection. Urine and fecal transmission are reduced if cages are kept clean and if sipper tubes or automatic waterers and hopper feeders are used instead of bowls, pans, or other feeding or watering devices that are easily contaminated with urine.

Public Health Significance

Several cases of suspected *Encephalitozoon* encephalitis have been reported in immunocompromised patients, and human-adapted strains of *E. cuniculi* exist. Because disease prevalence is high in meat rabbits, exposure risk may be high for abattoir workers. Owners, veterinarians, caregivers, and others should always wash their hands after handling or examining rabbits. Similarly, children and others handling rabbits in petting zoos or during animal assisted interventions should always clean their hands after handling rabbits or other animals.

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ENTERITIS AND RELATED CONDITIONS

General Discussion

Introduction

The gastrointestinal tract of rabbits and rodents is normally colonized by a complex array of symbionts and commensals that have important effects on immune function and nutrient uptake. Detailed studies have been conducted to characterize these populations in different animal species. Innate defenses, such as epithelial production of defensins, mucins, and various lectins, minimize bacterial overgrowth and maintain the mucosal barrier. Commensal populations of bacteria are important for tolerizing the gut to various antigens. The intestinal ecosystem is dynamic and also has spatial diversity.

The balance or imbalance of intestinal microorganisms may play a critical role in the development of disease. In a study of experimental ulcer formation associated with nonsteroidal antiinflammatory drugs (NSAIDs) in rats, factors released by Gram-positive bacteria (i.e., *Lactobacillus* spp.) in the small intestine appeared to play a protective role in impairing ulcer development. Conversely, NSAID-associated ileal ulcers were seen following overgrowth by Gram-negative enteric bacteria, and they were interpreted to play an important role in promoting ulcer development.

Gastroenteropathies in rabbits and other hindgut fermenting rodents such as guinea pigs, chinchillas, and hamsters result in nonspecific clinical signs and high mortality rates. The enduring challenge of determining the causes and pathogenesis of gastroenteropathies has resulted in confusion regarding potential treatments and prognosis. This causes considerable frustration for pet owners and for veterinary practitioners alike, because beyond the identification of an ongoing enteritis and offering of a guarded prognosis, the next step is generally to admit ignorance or to prescribe treatments that may be ineffective. Appropriate husbandry and diet are the most important measures to prevent enteropathies, and prevention is far more successful than treatment.

Etiology

There are a variety of events that may disrupt the microbial balance within the gut and lead to clinical disease. These include exposure to pathogenic organisms (viral, bacterial, and/or parasitic), therapy with narrow-spectrum antibiotics, and dietary or drug-induced alterations. Weanlings are most susceptible to enteric disruption because of the convergence of waning of passive maternal immunity, change in diet from high protein and fat (i.e., milk-based) to one that is high in fiber and fermentation-based, movement and separation of animals to new locations, and other species-specific factors discussed below.

Frequently two or more organisms may act in concert to produce disease. An additive effect in the intensity of the disease occurs in mice or rabbits co-infected with rotavirus and a pathogenic strain of *Escherichia coli*. Intestinal tract disease in rabbits is frequently attributable to dual infections with pathogenic bacteria (e.g., proliferative enterocolitis associated with an enteropathogenic strain of *E. coli* and *Lawsonia intracellularis*). A similar pattern has been observed in certain parasitic infections. For example, in outbreaks of intestinal coccidiosis in domestic rabbits, there may be a striking increase in the number of coliform bacteria in the intestine compared with those present in healthy animals. Similarly, when comparing the intensity of intestinal disease in germfree and conventional immunodeficient mice inoculated with *Cryptosporidium parvum*, impaired colonization and reduced intensity of disease were seen in mice with defined intestinal flora. These findings were attributed to nonspecific mechanisms provided by the commensal bacterial organisms.

Predisposition

The low pH (~1–2) of the rabbit stomach inhibits bacterial growth, such that the stomach and small intestine are essentially sterile. Weanling rabbits (3–14 weeks old) are very susceptible to diarrhea, in part because their stomach pH of 5–6.5 is not low enough to kill ingested bacteria; however, the higher pH permits them to acquire their gut flora. During lactation, milk components (8- and 10-carbon fatty acids) restrict intestinal microbial growth, but during the susceptible period, the naive gut and low gastric acidity favor passage and colonization by microbes, including potential pathogens. Adult rabbits may carry small populations of the same pathogens but are able to compensate for them because other commensal bacteria keep bacterial growth in check.

Predisposing factors for enteritis in all species include genetic background, concurrent infection, loss of maternal or acquired antibody, exposure to animals shedding pathogens, environmental stress, and dietary factors. Also, rabbit kits

weighing less than 60 g at birth are weaker and more susceptible to disease. In many cases of enteritis, particularly in the rabbit, the primary predisposing factors may be dietary. Excessive food consumption for any reason, including eating more in cold weather or return to full feed after kindling, may lead to premature and abrupt exposure to high-carbohydrate levels in the hindgut and predispose to enteritis, as may prolonged feeding of a diet low in fiber.

The pathogenesis of bacterial overgrowth is similar regardless of the species affected. Abnormal microbial action or other transitory chemical effects may lead to a fermentation-induced transient acidosis that reduces normal bacterial flora numbers and variety. This event is followed by a rising pH in the presence of high carbohydrates and proliferation or toxin production by certain bacteria. These events may cause gut hypomotility, which results in digesta retention and changes in substrate, bacterial populations, and osmolarity. Increased intestinal pH causes dissociation of volatile fatty acids, removing the inhibiting effect of undissociated fatty acids on bacterial proliferation. Additionally, a low-protein diet leads to a decrease in the number and size of Peyer's patches. This may result in decreased resistance to enteritis, while adverse stress leads to intestinal hypomotility and variable feed intake. Green feed, season of the year, water deprivation, changes in water salinity, and fiber particle size have uncertain roles in predisposing animals to enteritis.

Enteritis also may result from dysbiosis, leading to coliform or, more likely, clostridial proliferation after antibiotic administration. Antibiotics most often involved include orally administered procaine penicillin, ampicillin, lincomycin, amoxicillin, erythromycin and other macrolide antibiotics, cephalosporins, clindamycin, and other drugs that reduce certain Gram-positive flora. Diarrhea and other signs of enterotoxemia usually appear within 1–3 days of antibiotic administration and most cases result in death.

Clinical Signs

General signs of enteritis include sudden death with few clinical signs or, in animals living hours to days, anorexia, listlessness, rough hair coat, dehydration, polydipsia, bloat, borborygmus, weight loss, tooth grinding, diarrhea (Figure 5.9), and death. Feces are unformed, may be watery, soft, or tarry, have a foul odor, and may contain blood or mucus, and coprophagy often ceases. Rabbits may die within hours or days, or they may have abnormal stool and anal impaction over several months. Rabbits recovering from a bout of enteritis will often have profound production of mucoid stools.

Diarrhea can result from increased mucosal permeability (enterotoxemia, coccidiosis), hypersecretion (enterotoxemia), and malabsorption (viruses). Death occurs from loss of electrolytes and water, acidosis, and from the manifold effects of toxins.

Clinicopathologic changes include acidosis; decreased serum glucose, protein, albumin, calcium, and alkaline phosphatase; and increased serum aspartate transferase, blood urea nitrogen, phosphorus, cholesterol, and uric acid. Enterotoxic effects may lead to impaired metabolic pathways and renal and hepatic dysfunction.



FIGURE 5.9. Soiled hocks and perineum are a common presentation in rabbits with enteropathies. Courtesy of M. Brash.

Necropsy Findings

It is imperative during large-scale epizootics of enteropathy in breeding colonies or at production facilities that moribund animals be submitted alive to the pathology service for necropsy. Tissue decomposition in cases of enteritis is rapid, and optimal sampling of gut tissues for diagnostic purposes must be done as soon as possible after death if any hope of making a definitive diagnosis is entertained.

Gross signs of enteritis at necropsy include a discolored large intestine (gray-green is normal), fluid intestinal content with or without hemorrhage, and dehydration. A thickened corrugated appearance to the serosa may be indicative of *Lawnsonia intracellularis* infection (discussed elsewhere in this chapter). The additional findings of focal hepatic and myocardial necrosis may occur with Tyzzer's disease (discussed separately in this chapter), and cecal impaction may occur in rabbits with mucoid enteropathy.

Diagnosis

Except for a few enteric conditions linked to specific pathogens or signs (e.g., severe coccidiosis, salmonellosis, Tyzzer's disease), diagnoses are frequently challenging in cases or outbreaks of enteritis. Fecal flotation, smears, wet mounts of cecal smears, culture, histopathology, serology, and electron microscopy may all be useful techniques. Certain bacteria, such as *Clostridium difficile*, are ubiquitous and toxin elaboration must be demonstrated to correlate bacterial presence with a pathogenic effect.

Prevention

Prevention of enteritis is critically important. Primary preventive considerations include selection of healthy stock (from health records and initial and thorough diagnostic screening); proper

husbandry practices; strict sanitation; use of hopper feeders and sipper tube waterers; and, above all, appropriate management of feeding practices. Cages and equipment must be designed to prevent fecal contamination of feed and water and promote ease of sanitation by brush, water, heat, and chemicals. Nesting materials and boxes for young animals should be sanitizable, or preferably, disposable. Only if these practices fail should feed or water additives be considered as short-term measures. Vaccines for rotavirus and enterotoxemia (*Clostridium* spp) have been evaluated experimentally for rabbits but are not available commercially.

The current literature emphasizes the critical balance of fiber (lignocellulose) and carbohydrate (starch) in the feed and the ability to digest dietary carbohydrate to absorbable glucose before the starch reaches the cecum and colon, where it may be fermented. General measures to be observed are (1) dietary changes, especially changes in total carbohydrate consumed, should be gradual and made over 4–5 days; (2) dietary fiber should be kept between 17% and 23% to promote gut motility and dilute carbohydrate content; (3) feed should be restricted when a weaned litter is moved to a new cage; (4) feed to a recently delivered doe should be increased gradually to full feed; and (5) a higher fiber diet should be fed to young for the first 2 weeks postweaning and then gradually increased to higher-energy growth diets. All these critically important steps are intended to prevent undigested carbohydrate from passing into the large intestine.

Use of 250 ppm copper sulfate ($CuSO_4$) in the feed reduces mortality caused by enteritis based on the hypothesis that copper may interfere with clostridial growth and enterotoxin production. Higher fiber diets augment the copper effect. With $CuSO_4$ use, liver and fecal copper levels increase 20–30 times, but muscle copper level is unchanged.

Various commercial preparations of live or dead lactobacilli, other bacteria (e.g., *Streptococcus* spp., *Bacillus* spp.), yeasts, molds, acidifiers, and salts are available for use in meat rabbits and probiotic mixtures are added to either food or water. These products are purported to reduce weanling mortality, although the beneficial effect is more pronounced in colonies with higher incidences of enteritis. The postulated effects of these products in 3- to 10-week-old rabbits are to decrease intestinal pH, provide buffers, compete with pathogenic organisms, and provide amylase activity. Most lactobacilli added to the diet are killed in the highly acid environment of the rabbit's stomach, and if they do survive that passage, they are killed by bile, do not adhere to the intestinal wall, and do not colonize. Any beneficial mechanism, therefore, is unknown or unproven.

Off-label antibiotic mixtures (e.g., bacitracin-methylene disalicylate [BMD]), similar to those used for necrotic enteritis in chickens, are frequently added to commercial rabbit feed to manage or prevent ongoing enteritis issues. The responsibility for ensuring that no drug residues are present in meat produced for human consumption lies with the prescribing veterinarian and the producer.

Treatment

Because the disease process is usually advanced when clinical signs are first noted, treatment of enteropathies is often unrewarding. Elimination of the sickest animals and thorough equipment sanitization must accompany treatment of an infected herd. A fundamental step in treatment is to change the diet by increasing fiber and decreasing the protein-energy to some effective ratio of the two components (e.g., 14% crude protein and 20% crude fiber), which varies among colonies. Symptomatic treatment may be indicated for acute diarrheas in individual or colony animals. This consists primarily of maintaining hydration with appropriate warmed fluids given orally or parenterally, providing analgesics, maintaining core body temperature (38.5–40 °C), providing some form of enteral nutrition such as herbivore-specific critical care formula, and softening and removal of feces impacted around the anus. B vitamin supplements are often given because these animals are not practicing coprophagia. Because a specific etiologic diagnosis is difficult to determine, a balanced electrolyte solution such as lactated Ringer's solution is preferred, with or without added saline or glucose. The quantity given (IV, IO, PO, SC, or IP) is based on the usual calculation of degree of dehydration plus additional maintenance requirements. For example, a weanling rabbit (1–2 kg) with 10% weight loss would require 100–200 mL fluid above maintenance. Fluids given PO, SC, or IP can be divided and given as boluses three or four times a day. Fluids given by the intravenous or intraosseous route at the appropriate rate may be used to provide more rapid rehydration. Treatment for hypovolemic shock may also be indicated including high rate fluid therapy, vasopressors, colloids, and analgesics.

Body temperature can be maintained by placing the animal on a thermostatically controlled heating pad, by careful use of a heatlamp, by placing warmed oatbags or bags of warmed (25–30 °C) liquid around the convalescing animal, or using other small animal rewarming devices. Animals with enteritis are depressed and may grind their teeth, in part from visceral pain.

Beyond fluids, warmth, and possibly an analgesic to make the animal more comfortable, other treatments are unproven. Bismuth subsalicylate in a flavored medium may be given at 0.3–0.6 mL/kg every 4–6 hours (rabbits and rats will lick the suspension from a syringe tip), as may a 1 : 1 mixture of yogurt and a high-caloric supplement. Further down the list of useful treatments are antimicrobials, such as trimethoprim–sulfa (15 mg/kg every 12 hours), metronidazole (10–15 mg/kg every 12 hours), or any one of several sulfonamides. If clostridial enterotoxemia is suspected, IV or oral metronidazole may be given associated with drugs that may bind clostridial toxins such as cholestyramine or Bio-Sponge®. There is little evidence from controlled studies that these drugs, or any combination among them, are efficacious in resolving enteritis.

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Clostridial Enterotoxemia

Hosts

Fatal enterotoxemia due to *Clostridium* spp. proliferation and toxin production can occur in rabbits, hamsters, chinchillas, and guinea pigs either as a sporadic, spontaneous outbreak or following administration of one of several antimicrobials.

Etiology

Clostridial infections play an important role in intestinal disorders of laboratory and domestic animals. There are several predisposing factors recognized to contribute to the development of clinical disease due to these Gram-positive, anaerobic, spore-forming pathogens, particularly events that disrupt the normal microbial population. These include inappropriate antimicrobial administration and rapid dietary and environmental changes. Oral treatment with antimicrobials directed primarily against Gram-positive bacteria (e.g., penicillins, cephalosporins, and macrolides) has been associated with an overgrowth of *C. difficile* in guinea pigs, chinchillas, hamsters, gerbils, and rabbits.

The essential virulence factors of *C. difficile* are toxin A (a potent enterotoxin) and toxin B (a potent cytotoxin). The disease has a neural component as well, leading to release of substance P and subsequent mast cell degranulation. *C. difficile*–induced enterotoxemia is also reported in dogs (e.g., following metronidazole therapy for *Giardia* spp), nonhuman primates (e.g., following clindamycin therapy), and pigs. People and animals commonly carry *C. difficile* asymptomatically. The bacterial spores usually proliferate only after the disruption of the normal gut flora, for example, following antimicrobial treatment, because the normal flora competitively limits growth of *C. difficile* in healthy individuals. Because guinea pigs, chinchillas, and rabbits are hindgut fermenters, the antimicrobial-associated disruption in gut flora occurs primarily in the cecum and colon, resulting in profuse diarrhea associated with acute typhlocolitis. Colonization of the jejunum also occurs in rabbits, and death may be peracute. In hamsters, necrotizing typhlitis has been reported in animals fed an atherogenic diet. Hamsters are exquisitely sensitive to *C. difficile*, and clostridial enteropathies may occur in the absence of identifiable predisposing factors.

In rabbits fed a high-carbohydrate diet, clostridial enteropathy has been attributed to infections with either *C. perfringens* or *C. spiroforme*. *Clostridium spiroforme* is an anaerobic, Gram-positive, spore-forming, nonmotile, C-shaped bacillus. The bacilli may have a terminal spore body and may link end to end to produce helical forms. *C. spiroforme* may be the more important clostridial pathogen in rabbits. *C. perfringens* is classified into five types, A–E, based on production of one or more of the four major toxins (alpha, beta, epsilon, and iota). The syndrome following infection typically involves enterotoxemia and enteritis, usually involving the proximal gastrointestinal tract. Detection of enterotoxin in the feces of affected animals is the most sensitive means of confirming infection.

C. spiroforme causes iota enterotoxemia in rabbits, usually in the cecum. The toxin has two polypeptide components that act synergistically; one component may be an ADP-ribosylating enzyme and the other involved in cell surface binding. The toxin is produced within a pH range of 6.0–7.5 and depends on certain cations as cofactors for production or activation. It produces increased vascular permeability and is neutralized by specific antiserum. Outbreaks of clostridial enteropathy with mortality are common in commercial rabbitries and occasionally occur in the research environment. Increasing the fiber content of the feed may help to reduce the incidence of the disease.

Outbreaks of fatal diarrhea within 3–6 days or more after antimicrobial administration to guinea pigs and hamsters have been attributed to *C. difficile* and *C. sordellii*; these organisms also infect humans, hares, and other rodents. The cecal and colonic lesions are primarily necrotizing and hemorrhagic with or without mucosal hyperplasia. Spontaneous typhlitis resembling that induced by antibiotic administration has also been observed in an SPF guinea pig colony.

Administration of lincomycin may be associated with development of enterotoxemia in hamsters. Administration of lincomycin or clindamycin has also been associated with development of enterotoxemia in rabbits.

Transmission

Clostridium spp. are likely present in low numbers in the large intestine of rabbits and rodents. Transmission is primarily by the fecal–oral route, although clinical cases likely arise from proliferation of organisms already resident within the patient's cecum.

Predisposing Factors

Enterotoxemia in rabbits usually occurs in weanling fryers 4–8 weeks old when passively acquired maternal immunity has decreased, body growth is rapid, and intestinal microbes are populating the intestine. The disease, however, may also affect adults on high-caloric diets or does returning to full feed immediately after kindling. Factors described in the "General Discussion" section on "Enteropathies" are applicable.

Clinical Signs

The course of the disease is rapid in weanling rabbits. Affected animals may die with no other clinical signs, may develop and survive a mild diarrhea, or, more likely, over 6–48 hours may exhibit anorexia, polydipsia, immobility, profuse watery-to-hemorrhagic diarrhea, cyanosis, tooth grinding, hypothermia, recumbency, paralysis, or convulsions, and death. Mortality can be from a few to most colony animals, but a range of 25–60% is common. In older rabbits, such as does returning to full feed postkindling, deaths may be sporadic. Antibiotic-induced disease is primarily seen in adults treated for reasons other than for enteritis.

A "young doe syndrome" can occur in primiparous and early multiparous does and may be a form of clostridial enterotoxemia. Affected rabbits die suddenly when their litters are 1–4 weeks of age. A few days preceding death, the does go off feed, some salivate profusely, and diarrhea may or may not be seen.

The cause of neonatal or milk enterotoxemia is uncertain, but it may be caused by a toxin passed in low amounts through the milk or by *Clostridium* spp. passed into the neonatal gut. Young die suddenly during the first three days postpartum. This problem, which can produce great economic loss in a rabbitry, is more common during the winter months and may be linked with overfeeding of kits.

Hamsters with adult-onset *C. difficile* enteritis have diarrhea, dehydration, roughened hair coat, and a hunched posture. The most commonly encountered sign is profuse diarrhea. Animals with acute watery or hemorrhagic diarrhea have high mortality.

Necropsy Signs

C. spiroforme infection results in acute exudation, edema, and inflammatory cell infiltration followed by various degrees of mucosal necrosis and pseudomembrane formation. Portions of the small intestine, cecum, and colon are dilated and contain gas and watery brown, occasionally hemorrhagic, malodorous content. Petechiae and ecchymoses often are seen subserosally on the cecum, with hemorrhage and ulceration on the mucosal surface. Mucous exudation is rare. Proliferative changes of cryptal epithelium may occur, with clumps of desquamated cells in the lumen.

C. spiroforme is rarely isolated from healthy rabbits, and when the organism is identified its source presumably is the environment or spore-containing feed. Asymptomatic carriers exist.

Outbreaks of epizootic rabbit enteropathy have been described in commercial rabbitries by several groups across Europe in recent years. Mortality was described to be highest in weanlings (6- to 8-week-old animals). Grossly, there was marked diffuse dilatation of the gastrointestinal tract with liquid contents in affected animals. *E. coli* (nonenteropathogenic) and *C. perfringens* (alpha toxin positive) were the most common isolates from cecal samples. Coccidial oocysts were noted in feces of many animals, but no *Cryptosporidium* spp.

Histopathologically, in hamsters with *C. difficile* typhlitis, there is cecal necrosis, epithelial denudation, vascular congestion, and hemorrhage. More chronically affected hamsters have cecal mucosal hyperplasia.

Diagnosis

Diagnosis of clostridial enteropathy requires strict anaerobic culture conditions or demonstration of the enterotoxin from the feces. Identification of the typical Gram-positive coiled and curved organisms (*C. spiroforme*) on direct smear of the terminal ileum or cecum is a useful and rapid procedure assisting with confirming the diagnosis.

The primary methods for diagnosis include Gram staining of cecal smears (most practical but may be negative despite positive identification of cecal iota toxin), isolation of the toxigenic organisms on special media, cytotoxicity assays, and neutralization of toxic cecal filtrate with specific antiserum. The toxemia itself has been rarely, if ever, demonstrated, and a septicemia is not part of the disease.

A diagnosis is established by (1) correlating clinical signs and necropsy findings with age, medication, and treatment history; (2) performing diagnostic tests and ancillary procedures such as bacterial culture of cecal contents, especially for *E. coli*, *Salmonella* spp., and other enteric pathogens; (3) demonstrating organisms in histologic sections; or (4) demonstrating presence of toxin in intestinal contents.

Treatment

Treatment of clostridial diarrhea is discussed in this chapter under the "General Discussion" section for "Enteropathies." There is little to no evidence that antimicrobials are effective or helpful in treating individual cases or outbreaks of enterotoxemia.

Supportive treatment should be started and antimicrobials withdrawn immediately in animals that develop diarrhea during antibiotic treatment. Shock treatment with high rate fluid therapy, correction of electrolytic and acid–base imbalances, and the use of vasopressors and systemic antibiotics may help in some cases. Cholestyramine (Questran®) at 2 g/20 mL water, PO, every 24 hours has been demonstrated to bind to clostridial and other bacterial toxins in humans and may be useful in rabbits.

Prevention

Prevention of *C. spiroforme* enteritis follows the general recommendations discussed previously. As mentioned, when reviewed over a range of different trials, antimicrobial administration is

not efficacious in preventing the disease and may exacerbate an existing problem. An experimental bacterin prepared from a formalinized, alum-precipitated antigen (antitoxin) has been used to protect against an intraperitoneal challenge of *C. spiroforme* toxin. The vaccine was given to rabbits at weaning and boosted 14 days later. No protection was passed to the young. Antibody levels detected by ELISA plateaued at 17 days and remained at that level throughout the 42-day trial.

"Young doe syndrome" can be prevented by increasing the amount of feed provided after kindling by 10–25 g per day, rather than all at once, until ad libitum levels are reached.

Public Health Significance

Whereas *C. perfringens* affects a variety of species, *C. spiroforme* is primarily a rabbit pathogen, although this clostridium has been associated with diarrhea in one human case report. *C. difficile* is a spore-forming, Gram-variable bacterium that has been identified as part of the gut flora in neonatal humans, and it is considered normal indigenous gut flora of young mammals of several species, including the hamster, rabbit, and guinea pig. Generally, the bacterium causes no clinical signs unless there is bacterial overgrowth. *C. difficile* has also been associated with a range of serious gastrointestinal illnesses in humans and is considered to be an emerging zoonotic disease. Recent studies involving PCR ribotyping of *C. difficile* from a range of species, including pigs, dogs, and horses, have demonstrated identical types in these species and in humans. It is unknown whether rabbits may be a reservoir for *C. difficile* ribotypes relevant for humans.

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Colibacillosis

Hosts

E. coli is the most common etiologic agent for diarrhea in animals. Rabbits and rodent species of all ages may be affected by enteritis induced by the bacterium.

Etiology

There are seven classes of pathogenic *E. coli*, including enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), diarrhea-associated hemolytic *E. coli* (DHEC), and cytolethal descending toxin (CDT)-producing *E. coli*. Many pathogenic *E. coli* are capable of producing heat-stabile or heat-labile toxins. The heat-labile toxin closely resembles cholera toxin. The toxins are elaborated directly into the cytoplasm of the cell, where they induce increased cell permeability leading to cell death. Additional virulence factors of EPEC strains include secretion of a collection of proteins that interfere with the host cell metabolism; ETEC strains adhere to intestinal epithelial cells and produce enterotoxins that cause cell death and a secretory diarrhea; EIEC strains invade and multiply in enterocytes, causing exudative enteritis and endotoxemia; and EHEC (attaching and effacing) embed in enterocyte cytoplasmic membranes, efface microvilli, and produce a Shiga-like toxin, with resulting damage to the mucosa, inducing hemorrhage and diarrhea.

Younger animals are particularly susceptible to coliform infections. The clinical signs associated with a pathogenic coliform infection (severe watery-to-hemorrhagic diarrhea with anorexia and wasting) may be attributable solely to the organism, but frequently other microorganisms are involved in the disease process. For example, in domestic rabbits, an outbreak of diarrhea in suckling or weanling animals may be attributable only to infection with EHEC. In other cases, there may be two or more pathogens acting in concert to produce clinical disease. Concurrent infections with a pathogenic strain of *E. coli* have been shown to have an additive effect in animals infected with rotavirus or intestinal coccidiosis. It is likely that strains of *E. coli* play a similar additive role in mixed microbial infections in other species. Immunodeficient animals may be particularly at risk. In laboratory rodents, enteritis due to EIEC has been reported in immunocompromised mice.

The causative agents in rabbits are among the hundreds of biotypes or serotypes of the Gram-negative, facultatively anaerobic bacteria. Pathogenic serotypes of *E. coli* cultured from rabbits with acute diarrhea include 015, 0153, 0157, 0128, and an unclassified serogroup OX1; however, other types, some thought to be nonpathogenic, also have been cultured during diarrheal outbreaks. The gastrointestinal tracts of rabbits, guinea pigs, and gerbils normally have few or no *E. coli*, whereas other rodents carry the organism in low numbers.

Other probable coliform diseases in small rodents include diarrhea in gerbils and enteritis in hamsters, which may occur alone or in combination with a proliferative or hyperplastic lesion of the ileum. After antibiotic injections, guinea pigs and hamsters may die within 2–6 days; coliform or clostridial overgrowth has been implicated as the cause.

Transmission

Transmission of *E. coli* is by the fecal–oral route. The clinical disease, however, probably develops from activation of a preexisting component of the intestinal flora.

Predisposing Factors

Predisposing factors for colibacillosis include change of diet, entrance of pathogenic organisms into the uncolonized gut of weanlings, high-carbohydrate–low-fiber diets, adverse stress such as chilling of neonates, cecal pH greater than 6.8, other disease, or alteration of the microflora with antibiotics active against Gram-positive or anaerobic bacteria. Factors that predispose to diarrhea or other enteropathies in rabbits and rodents are discussed in more detail in the "General Discussion" section for "Enteropathies" in this chapter.

Clinical Signs

Signs attributed to *E. coli* infection may be similar to those of other enteric infections, and the signs and lesions of experimental *E. coli* infections in healthy rabbits and rodents range from mild to severe (Figure 5.10). Morbidity and mortality can range from mild transient diarrhea in a few young animals to death of entire litters from profuse, watery, and bloody diarrhea. Early nonspecific signs of colibacillosis include acute onset, fever, depression, reduced water and food intake, weight loss, and peracute death within 6–72 hours of infection. Within hours or a few days, perineal staining occurs with watery, foul-smelling brown-to-yellow diarrhea, sometimes with blood and mucus. Because of the effects of various *E. coli* serotypes and of receptor maturation, outbreaks may be seen in sucklings, weanlings, or adults. Signs in all groups vary from mild to severe, and death may occur within hours of appearance of signs to several weeks later.

Necropsy Signs

Depending on the strain of *E. coli* involved, lesions may be confined primarily to the small or large intestine. Microscopically, identifiable bacilli may be evident lining the mucosal surface in close apposition to the microvilli, and there is swelling and sloughing of enterocytes in affected regions. Effacement of the mucosa and villous atrophy is a typical change seen during the acute stages of the disease. Diarrhea is usually accompanied by dehydration and electrolyte imbalance in affected hosts, with variable mortality. Persistent infections may occur, particularly in immunocompromised animals. Gross signs of colibacillosis include cecal hemorrhage and edema and a watery brown, fetid, luminal content. Other nonspecific changes include enlarged mesenteric nodes and congested kidneys. Microscopically, there are hemorrhages and edema within the gut wall, loss of epithelium, and inflammatory infiltrates within the submucosa and mucosa.



FIGURE 5.10. Coliform enteritis in a weanling rabbit. Note the flaccid, fluid-filled loops of small intestine.

Diagnosis

Specific diagnosis is through clinical signs and isolation of pathogenic strains of *E. coli* classified by culture, microscopy, serotype, and biotype. Demonstration of bacterial attachment and effacement of intestinal epithelium further confirm the diagnosis. The most practical method is culture of feces on MacConkey's medium and recovery of nonhemolytic, facultatively anaerobic *E. coli*. Samples must be fresh for optimal results.

Treatment

Infection with EPEC strains of low pathogenicity can be treated symptomatically and with strict hygienic measures, including vigorous culling of dehydrated and obviously sick young and thorough washing and disinfection of the environment. Chloramphenicol may be useful in some circumstances, and supportive care for dehydration and general debility can be helpful in management of individual cases.

Prevention

Prevention of colibacillosis follows the recommendations in the "General Discussion" section on "Enteropathies" in this chapter. Highly pathogenic coliforms, either in sucklings or in weanlings, are difficult to eliminate, and destruction of the affected colony may be necessary.

An orally administered enteric-coated protease preparation to prevent ETEC attachment and a formalin-killed bacterin given per os over 10 days to stimulate local and systemic responses have been tested to reduce the coliform component of the enteritis complex, but neither product is available commercially. Trials using large populations of live *Lactobacillus acidophilus* or *L. bulgaricus* have inhibited ETEC effects, but their preventive effects on EPEC infection are unreported.

Public Health Significance

It is important to note that EHEC is considered to be an emerging human pathogen. Rabbits, both from pet and commercial sources, are reported to be reservoirs of this bacterium and

may carry EHEC subclinically. Experimental infection of rabbits with EHEC has led to renal hypoxia and damage, similar to what is seen in humans with hemolytic uremic syndrome (HUS). Appropriate hand washing is required after handling or examining sick animals to minimize the risk of disease transmission.

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Mucoid Enteropathy

Hosts

Mucoid enteropathy (ME) of rabbits is a distinct disease with unusual characteristics and, in this description, is not a catarrhal diarrhea. The disease occurs in adults, but weanling rabbits 7–10 weeks of age are the most susceptible.

Etiology

Much has been written about ME. Research reports and reviews contain descriptions of numerous methods for diagnosis and prevention, but little is certain as to its etiology or treatment. The disease is characterized by hypersecretion, minimal inflammation, and accumulation of mucus in the small and large intestines. Mucoid enteropathy may occur concurrent with other enteric diseases such as coccidiosis, clostridial enterotoxemia, Tyzzer's disease, and colibacillosis, which obscure the classic signs of ME.

The etiology of mucoid enteropathy remains unknown. When serum (but not plasma) of rabbits with mucoid enteropathy is placed on the free-living, mucus-secreting coelomate, *Sipunculus nudus*, the urn cells of that invertebrate secrete copious mucus. Mucus-stimulating substance (MSS), a postulated blood-borne factor, adheres to certain cell receptors and elicits mucus release. In ME, the lectin-binding activity of colon goblet cell mucin is altered from that of normal mucin.

Transmission

If an infectious organism or its enterotoxin is involved, transmission is most likely by the fecal–oral route. Sterile cecal filtrates stimulate excessive mucus production in colonic mucosal explants, suggesting transmission of a physical factor.

Predisposing Factors

Dietary changes, dietary fiber less than 6% or greater than 22%, antibiotic influences, environmental stress, and encounters with bacteria are all considered factors predisposing to ME. The disease is more common in the spring, in certain rabbit families, in young does with their first litter, in does with large litters, and in young fryers with high food intake.

Clinical Signs

Disease outbreaks diagnosed as ME have occurred in both weanling (4–12 weeks old) and adult animals. Abdominal distention, slushing of intestinal contents, lethargy, hunched posture, polydipsia, rough hair coat, tooth grinding, rapid weight loss from anorexia and diarrhea, dehydration, clear or yellow-brown mucus diarrhea, staining of the perineum, subnormal temperature (37.2–38.3 °C; normal is 38.9–40 °C), cold extremities, and death may be seen in cases of ME, although many of these signs are common to other enteropathies. Distinguishing signs of the condition are the subnormal temperature, copious quantities of clear mucus diarrhea sometimes preceded by constipation, occurrence in adults, and necropsy signs.

Clinical signs precede death by 1–3 days in an acute form, which is nearly indistinguishable from other enteropathies, or by 7–9 days in the longer-term condition. As the disease progresses, mucoid diarrhea becomes profuse or constipation occurs, and in either case animals die. Weight loss may reach 20–25% of original body weight. Mortality may reach 70% or more, with no sex differences. Does with litters in the nest box may succumb. Abdominal palpation may reveal a firm, impacted cecum or ballotable fluid-filled intestines.

Clinical laboratory findings are those associated typically with dehydration, for example, increased hematocrit. Depending on the stage of the disease, total leukocyte counts, serum lipase, glucose, albumin, globulins, phosphorus, and blood urea nitrogen may be elevated. Calcium, potassium, sodium, and chloride may be decreased.

Necropsy Signs

Lesions of subacute, uncomplicated mucoid enteropathy are derived from the hypersecretion of electrolytes, water, and mucus from ostensibly normal epithelium, or at most from an epithelium with mild edema and slight-to-moderate mixed inflammatory cell infiltration. The esophagus and stomach are usually free of lesions. The small intestine is either empty or contains fluid and mucus with a progressive increase in goblet cell size and number from the duodenum to ileum (Figure 5.11).



FIGURE 5.11. Section of opened intestine from a rabbit with mucoid enteropathy.

In acute (1–3 days) stages, the digestive tract contains a watery fluid with pockets of gas. In these stages, the cecum, lymphoid appendix, sacculus rotundus, colon, gallbladder, bile ducts, pancreatic ducts, and even the tracheal mucosa exhibit characteristic goblet cell hyperplasia and increased mucus-secreting activity.

The excessive discharge of mucus (mixture of neutral and acidic mucins, proteins, cells, bacteria, ions, and water), especially into the colon and distal ileum, results in formation of a clear to yellow, semi-fluid to gel plug that can be removed in large masses from an opened colon at necropsy. The jelly mass in some rabbits may be mixed with chyme or secreted fluid, resulting in a colored discharge from the rectum.

A critical gross lesion of uncomplicated mucoid enteropathy in the longer-term stages is an inspissated, firm, dry or clay-like mass of ingesta filling the cecum, adhering to the cecal wall, and possibly obstructing the ileo-cecal junction. The static cecal mass and the gelatinous colonic plug underlie constipation. Goblet cell ducts are depleted of acidic mucus and are plugged and dilated. Death follows ileus and impaction.

Histologically, the primary change is goblet cell hyperplasia of the ileum, cecum, appendix, sacculated colon, and colon.

Diagnosis

Diagnosis of ME is based on clinical and necropsy signs. Culture of the gut or a fecal examination may be indicated to detect or rule out clostridial infections, colibacillosis, salmonellosis, coccidiosis, and other parasitic diseases.

Treatment

Intense fluid therapy given by stomach tube or subcutaneously, coupled with an enema or laxative to remove the mucus mass, may help in some cases, as may antibiotic administration to control bacterial overgrowth. The prognosis is generally poor in most cases, but antibiotics, fluids, electrolyte solutions, vitamins, and analgesics can be tried.

Prevention

The usual recommendations to prevent enteritis in rabbits apply to the prevention of mucoid enteropathy as well; fiber should be added to the diet, but not more than 22% crude fiber because in one case, higher fiber seemed to predispose to the disease.

Public Health Significance

There is no known public health hazard with ME.

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EPILEPSY IN GERBILS

Etiology

Companion animal owners, animal technicians, and others not familiar with gerbils may become alarmed on witnessing, for the first time, the spontaneous tonic–clonic seizures or convulsions seen commonly in gerbils. These reflex epileptiform seizures are precipitated by novel or excitement-producing experiences such as handling and unfamiliar environments.

Predisposing Factors

Seizure-resistant and seizure-sensitive strains of gerbils exist. Incidence of seizure susceptibility in normal populations is approximately 20% but approaches 100% in some lines. Seizure traits may be influenced as well by cage, diet, age, and environmental determinants. Adverse stress decreases the threshold to trigger seizures in adults.

Clinical Signs

Seizures vary from a mild hypnotic state characterized by cessation of motor activity and spasms or twitching of vibrissae and pinnae to severe myoclonic convulsions followed by tonic extensor rigidity and body flattening. Violent kicking of the hind legs occurs after the seizure motor manifestation has faded. Seizures last from approximately 30 seconds to

2 minutes. Gerbils begin having seizures at approximately 45 days of age, although the onset is extremely variable. Usually the refractory period following a severe seizure is several days and may be due to an adaptation or habituation effect. Although the characteristic clinical signs appear severe, there are no apparent lasting or long-term adverse effects and normal activity is resumed within a few minutes.

Diagnosis

Characteristic clinical signs and ease of inducing such signs consistently are adequate information for a presumptive diagnosis of epilepsy. Differential diagnoses should include encephalitis, poisoning, toxemia, and trauma in all cases of convulsions.

Prevention and Treatment

Frequent handling from an early age may suppress development of seizures. Phenobarbital has been evaluated experimentally for seizure control in gerbils; however, efficacious doses of anticonvulsant drugs for pets have not been reported and these drugs are generally not recommended because of the short duration of most seizures. Levetiracetam may also be useful in gerbils with this condition.

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FILOBACTER RODENTIUM INFECTIONS (CILIA-ASSOCIATED RESPIRATORY BACILLUS)

Hosts

Naturally occurring infections by *Filobacter rodentium* (previously known as cilia-associated respiratory bacillus or CARB) have been reported in wild and domestic rats, mice, rabbits, guinea pigs, hamsters, cattle, goats, swine, cats, and dogs.

Etiology

F. rodentium is a Gram-negative, agyrophilic, motile, nonspore-forming, bacterium in the *Flavibacter/Flexibacter* family. While many species of animals can be infected by the bacterium, the strains affecting rabbits and rats are species-specific and share less than 50% sequence homology. Similarly, isolates of rat origin are more pathogenic for mice than were those of rabbit origin.

The bacterium is capable of colonizing the respiratory tract (upper nasal respiratory passages, trachea, lungs, and middle ear) and acting as a primary pathogen as well as exacerbating infections caused by other agents. Pathogenicity is highly correlated with bacterial strain, and in experimental *F. rodentium* infections in rats, there was little difference in susceptibility to infection between F344, Lewis, and Sprague-Dawley rats.

Predisposing Factors

Host species, *F. rodentium* substrain (e.g., rat or rabbit origin), and the presence of other respiratory pathogens such as *P. multocida* and *Mycoplasma pulmonis*, acting as co-pathogens, are factors that predispose to clinical disease. Results of pathogenesis studies, using an isolate of mouse origin, suggested that mice are highly susceptible, followed by hamsters, rabbits, and guinea pigs (rats were not evaluated). Sex and age of the animal did not seem to influence susceptibility to the bacterium. Use of a homologous strain of *F. rodentium* (mouse origin) likely skewed the study results.

Transmission

Transmission is primarily by direct contact with infected animals, that is, dam to suckling offspring. Interspecies transmission does occur, but pathogenicity of the organism may be more variable and is generally less virulent in a non-homologous host. Experimental inoculation of rabbits with rat-origin *F. rodentium* resulted in seroconversion without histopathologic lesions. Experimental infection was accomplished by using lung homogenate of infected animals, *F. rodentium* cultured in embryonated ova, or organisms grown on artificial media. Airborne transmission is an unlikely route for spread of infection.

Clinical Signs

Experimentally transmitted and naturally occurring uncomplicated *F. rodentium* infections have similar clinicopathologic characteristics. Although infected rodents are often asymptomatic, signs such as increased respiratory noises, for example, wheezing and crackling, decreased activity, weight loss, and rough hair coat may be observed.

Necropsy Signs

Necropsy signs are variable and will depend upon the pathogenicity of the bacterial strain involved and the chronicity of the infection. In some cases in rabbits, no gross lesions were associated with natural infection by *F. rodentium* nor

were lesions present in rabbits and guinea pigs experimentally inoculated with rat-origin *F. rodentium*. Nonspecific gross lesions in the lungs, including failure to deflate (emphysema), areas of consolidation and atelectasis, scattered pale foci on the pleural surface, and clear-to-mucoid exudate in the trachea have been reported in infected rabbits.

A multifocal-to-coalescing pyogranulomatous bronchopneumonia with bronchiectasis, enlarged mediastinal and bronchial lymph nodes, and dilated bronchi is seen in naturally infected rats and mice and in experimentally infected hamsters.

Histopathologic lesions attributed to *F. rodentium* infection vary between and within species. The bacilli are argyrophilic and readily detected with a Warthin–Starry stain. Consistent findings include observation of *F. rodentium* interdigitating between cilia in ciliated respiratory epithelial cells with a moderate-to-marked mixed inflammatory infiltrate in the lamina propria around bronchi and bronchioles. The location of the organisms leads to interference with the mucociliary apparatus, and there may be secondary infection with other opportunistic agents in chronic cases. More severe and advanced lesions in rats include thickening of the bronchiolar epithelium with goblet cell proliferation, sloughing of epithelial cells, and bronchiectasis. Pyogranulomatous bronchopneumonia and tympanitis are reported in rats.

In rabbits, *F. rodentium* infection causes mild hypertrophy and hyperplasia of the laryngeal, tracheal, and bronchial epithelium with few, if any, damaged cilia. There is a concurrent mild inflammatory infiltrate composed of heterophils, lymphocytes, and plasma cells in the lamina propria.

Diagnosis

In laboratory animal facilities, a soiled bedding transfer sentinel system may not detect the presence of the bacterium. Direct contact is required between the sentinels and the affected animals for efficient transfer of the bacilli. A PCR confirmatory assay is available and is rapid, specific, and sensitive for diagnosis of *F. rodentium* strains of rats and mice. Serological tests, such as ELISA and IFA, are sensitive in detecting serum antibodies to *F. rodentium*, but they lack specificity. Histopathologic examinations of formalin-fixed, decalcified, silver-stained sections of the respiratory tract are useful to confirm presence of the bacilli between cilia in the epithelium of the trachea, lungs, and nasal turbinates. *F. rodentium* can be cultured in artificial media and examined using electron microscopy for ultrastructural morphology. Other characteristics such as PAS-positive, Gram-negative, nonacid-fast, and nonspore-forming habits offer methods for additional diagnostic confirmation.

Treatment

Culture and antibiotic sensitivity testing have demonstrated that *F. rodentium* is sensitive to sulfonamides (sulfamethazine), procaine penicillin G, ampicillin, neomycin, gentamicin, and streptomycin. Many of these agents can be given in the water. No data exist to show the efficacy of antimicrobial therapy in eliminating *F. rodentium* from enzootically infected colonies or in chronically infected pets. In such cases, antibiotic treatment may be intermittent and palliative. Other complicating factors and diseases should not be overlooked when attempting to treat *F. rodentium* infections.

Prevention

Routine serologic screening, using animals from *F. rodentium*-free colonies for replacement breeders or as pets, and excellent husbandry practices are suitable control measures. Other measures are quarantine and isolation of infected animals and cesarean rederivation of valuable replacements.

Public Health Significance

F. rodentium infection or disease has not been reported in humans, to date.

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GASTROINTESTINAL STASIS IN RABBITS

Hosts

Previously, gastrointestinal stasis in rabbits and other small mammal pets was thought to be due to accumulation of masses of hair in the stomach (trichobezoar or "wool block"

in Angora rabbits). This was confusing for the practitioner, in terms of etiology, because rabbits may have large gastric hair balls and never show clinical signs, they may have a small, obstructing hair mass in the pylorus and die, or they may show all or most clinical signs ordinarily associated with an obstructive gastric mass yet have no obvious gastric or duodenal blockage. More recent evidence suggests that hair accumulates in the stomach because of an underlying motility disorder known as gastrointestinal stasis. However, whether there is a primary or secondary functional ileus in "gastrointestinal stasis" cases is still a matter for debate and controversies. Prognosis is often guarded in cases of prolonged gastric or intestinal hypomotility.

Etiology and Predisposing Factors

Gastrointestinal stasis is not a disease in itself but a term used colloquially to refer to anorexic rabbits with decreased fecal output. Gastrointestinal stasis generally arises because of defects in propulsion (hypomotility), because of obstructions or because of other conditions leading to anorexia. Hypomotility can be caused by low-fiber:high-carbohydrate diets, obesity, lack of exercise, pain, or a variety of management or psychological stressors. Dental disease is also an important cause for anorexia predisposing to functional ileus. Any disease leading to pain or general discomfort may cause gastrointestinal stasis such as urolithiasis, renal disease, otitis, dental disease, neoplasia, or anesthesia, among many factors. Obstructions may result from impaction of ingested hair or foreign bodies combined with chronic dehydration.

Gastrointestinal stasis leads to anorexia, lethargy, ileus, constipation, and, occasionally, rupture of the intestine with subsequent peritonitis and death. Rough handling, molting, and ingestion of large amounts of fur are other predisposing factors.

Clinical Signs

The pattern of signs suggesting gastrointestinal stasis or obstruction is a lack of interest in food, anorexia, progressive emaciation, increased water consumption, and scant feces. These signs may also occur with dental disease, oral or esophageal abscesses, pain, loss of sense of smell, foul-smelling feed, heat stress, lack of access to drinking water, and various systemic diseases. The stomach is usually readily palpated and may feel distended and doughy. Emaciation can be determined by comparing hypaxial muscle mass among rabbits.

Necropsy

Hair found normally in a rabbit's stomach is loose and mixed with food or cecotrophs. When collections of entangled, matted, and compacted hair are retained in the stomach, they become trichobezoars (Figure 5.12). There may be several trichobezoars, most weighing 6 g or less, or a large mass may fill the fundus and extend into the pylorus. Most hair balls reported weigh between 1 g and 24 g, but they can weigh over 100 g. The mass or masses may be loose or firm, but most are soft yet cohesive.



FIGURE 5.12. Post mortem specimen from an anorectic rabbit with gastrointestinal stasis. There is accumulation of hair within the stomach.

Associated lesions include focal gastric hyperemia, inflammation, and ulceration; hepatic lipidosis due to obesity; and, rarely, ante mortem gastric rupture and peritonitis.

Diagnosis

Ante mortem determination of a gastrointestinal obstruction can be difficult. Clinical signs of progressive emaciation and absence of fecal pellets are important indications. The presence of a very large fluid-filled stomach on radiographs in conjunction with hypochloremic metabolic alkalosis and hyperglycemia are strong indications for gastric outflow or duodenal obstruction in rabbits. Whether or not trichobezoars are palpable is debatable, but a large, firm mass in the epigastric region of the abdomen should receive attention. Soft or smaller nodules cannot be distinguished from other stomach contents, especially masses of mucus-linked cecotrophs. Palpation may rupture an inflamed stomach.

Contrast radiography would seem to be useful, but results are often inconclusive, especially if the material is in the pylorus or if cecotrophs are present. Radiologic procedures that have been described are per os administration of (1) 30 mL liquid barium sulfate followed by radiographs taken at 300 MA, 84 KY, 0.05 seconds, at 36 in, or (2) 15 mL of liquid barium sulfate, rolling the rabbit to disperse the medium, and then delivery of 60 mL air. A 5–8 Fr pediatric feeding tube can be readily passed through the ventral meatus of the nose into the stomach to facilitate delivery of contrast material. Abdominal ultrasound examination is helpful at diagnosing gastric outflow obstruction, duodenal obstruction, cecal impaction, appendicitis, and detecting other lesions that could cause anorexia in rabbits. CT scan is also useful in detecting obstruction anywhere in the gastrointestinal tract.

Treatment

Following diagnosis, medical treatment for suspected gastrointestinal stasis should be considered urgent. Animals are often fragile at this point and must be handled gently. Aggressive fluid therapy is indicated to rehydrate obstructive gastric masses. In addition, animals may require analgesics such as meloxicam (0.5 mg/kg PO 1–2 times daily) as well as promotility agents (e.g., metoclopramide, 0.5 mg/kg PO or SC 1–3 times daily), provided that a complete obstruction is not suspected. Nasogastric or syringe feeding of liquid herbivore critical care supplements is necessary to provide nutritional support. Percutaneous pharyngostomy tubes have been used for force-feeding rabbits and are generally well tolerated, although they may require an Elizabethan collar for protection. In severe non-obstructive cases or distal obstructive cases, a more aggressive approach is needed including intravenous fluid therapy (tailored to electrolyte and acid–base disorders and endpoints of hypovolemia), a gastrointestinal motility drug (lidocaine CRI at 30–100 µg/kg/min), pain medication (fentanyl or ketamine CRI or buprenorphine SC q8h), and IV antimicrobials (see Chapter 3 for CRI dosages). Force-feeding should be delayed until the patient is stabilized. Stomach decompression under deep sedation using a flexible tube introduced orally into the stomach may also be indicated.

Gastrotomy to remove stomach masses carries a poor prognosis and should be a last resort. However, a gastrotomy is needed when signs of obstructions are present. Pre- and postsurgical supportive therapy should be intense and should include parenteral fluids (e.g., lactated Ringer's), pain medication, and an antibiotic (e.g., trimethoprim–sulfa, 15–30 mg/kg twice daily, IM or PO). The stomach is elevated with stay sutures through a 4-cm cranial celiotomy incision, and an incision made on the greater curvature. The hair masses are removed and the incisions closed. Rabbits usually continue to be anorectic for up to several days postoperatively, and the rabbit may have to be forcefed a critical care diet or fed via a nasogastric tube (30 mL per feeding). Various vegetables, canned pumpkin, and moistened rabbit feed slurry have also been recommended. To prevent recurrence, the rabbit should be fed a high-fiber feed or given supplemental hay, as well as opportunities for exercise.

Prevention

Avoiding stress and obesity, provision of a high-fiber low-calorie feed and ad lib palatable water, careful restraint, routine grooming (brushing or clipping) to remove excess hair, and environmental enrichment are reasonable recommendations for prevention.

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HANTAVIRUS INFECTIONS

Hosts

Rodents are the primary reservoir hosts worldwide of the Hantaan and related viruses that cause hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS). Susceptible reservoir rodents include *Rattus norvegicus* and *R. rattus* (rats), *Peromyscus* spp. (white-footed mouse), and *Microtus* spp. (voles) in the United States, and *Clethrionomys* spp. (voles) and *Apodemus* spp. (field mice) in other parts of the world. In research settings, the rat is the primary animal associated with spread of hantaviruses. Rabbits, guinea pigs, cats, and dogs have been found to be seropositive occasionally when kept in the same room as infected rats.

Mice may become infected with hantaviruses, and wild mice such as *Peromyscus maniculatus* have been identified as the primary hantavirus reservoir and cause of HFRS outbreaks in humans in the US Southwest. Humans are considered to be accidental hosts.

Etiology

Both HFRS and HPS are caused by infection with one of the hantaviruses of the arthropod-borne family, Bunyaviridae. HFRS refers to a group of clinically similar diseases that occur throughout Europe and Asia. Hantaviruses that can cause HFRS include Hantaan virus, Puumala virus, Dobrava virus, and Seoul virus. HFRS is a febrile disease with renal involvement that has occurred primarily among researchers and animal technicians working with infected rats or cell cultures.

HPS refers to a clinical syndrome caused by a number of hantaviruses in North and South America. In the United States, the Sin Nombre virus causes most cases of this condition, and increases in seroprevalence in mice occur in certain years when forage is plentiful. HPS can also be due to infection by at least 11 other named and unnamed hantaviruses.

Transmission

Hantaviruses infect most major wild mouse and rat populations in the United States. Seroepidemiologic studies suggest an antibody prevalence rate of up to 8% in wild murids. Infected rodents shed virus in saliva, urine, and feces for many weeks, and possibly the infection persists for a lifetime, but the duration of shedding and infectivity is unknown. The average incubation period is 12–16 days. The virus is probably not transmitted directly between humans.

Biting may be an important mode of transmission among free-living rodents because of infectious virus in saliva. Transmission may also occur by contact with fomites contaminated with rodent excreta or urine, by direct introduction into broken skin or the conjunctiva, by ingestion of contaminated food or water, or by aerosols.

Predisposing Factors

Predisposing factors among rodents include fighting, biting, and possibly grooming. There is no significant difference in survival, growth rate, body size, and fertility between seronegative and seropositive wild-caught brown Norway rats, and the virus appears to have little or no impact on demographics in Norway rat populations.

Clinical Signs

Clinical signs and lesions have not been reported in laboratory rats or mice, although they develop high antibody titers.

Diagnosis

Hantaviral infection can be diagnosed by detection of specific serum antibodies with ELISA techniques.

Prevention

The best approach to disease control and prevention is risk reduction through environmental hygiene practices that deter wild rodents from colonizing homes, laboratory buildings, and work environments. Control of wild rodents without concurrent control of fleas may increase risk of human plague as rodent fleas seek an alternative food source. Routes by which wild rodents might contaminate laboratory stocks must be eliminated. Laboratory work with these viruses must be done under appropriate conditions for controlling hazardous Biosafety Level 3 agents. Testing for hantaviruses should be conducted when potentially infected laboratory rats and possibly other rodent species are to be shipped from Asia, the United Kingdom, France, and Belgium or other areas of the world where the viruses may exist to other uninfected countries and areas. Testing should be done in advance of shipment or during quarantine of the animals after arrival. Wild-caught mice of the genera mentioned previously should also be tested, particularly if they originate from locations where the virus is known to be endemic.

Areas in which hantaviruses are being studied must be sanitized appropriately. Hantaviruses are susceptible to 1% sodium hypochlorite, 2% glutaraldehyde, and 70% ethanol. A 10% sodium hypochlorite solution has been recommended for heavily soiled areas. Hantaviruses are also susceptible to acid (pH 5) conditions and can be inactivated by heating at 60 °C (140 °F) for 1 hour.

Public Health Significance

Although not likely to cause clinical disease in rodents, hantaviruses may cause serious disease and death in humans. Clinical features of HFRS in people include acute high fever, severe malaise, myalgia, headaches, diarrhea, nausea and vomiting, proteinuria, oliguria, hemorrhagic manifestations, and possibly death. Companion animals should not be allowed to contact wild rodents or their droppings because of the risk for disease transmission.

Laboratory personnel have contracted disease from infected laboratory rats in Japan, France, Belgium, Korea, and Singapore. When detected in a facility, the entire colony of animals must be assumed to have similar exposure and should be depopulated. Most infections in humans result from aerosols generated by infected rodents or when dried rodent droppings have been disturbed in rural residences, garages, and sheds during spring cleaning. Wearing respiratory protection is advised for these procedures to reduce risk. Worldwide, lymphocytic choriomeningitis and hantavirus infections are potentially the most important zoonotic pathogens of laboratory rodents that do not originate from known negative sources. SPF rats and mice are of little risk for transmission of these pathogens. Feral rodents are not recommended as pets for this reason.

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HEART CONDITONS

General discussion

Rabbits and rodents have been bred and worked with in science for greater than 100 years and most experiments enroll young, healthy adult animals for relatively short durations. Aging conditions are rarely encountered unless they are the specific focus of the study. Further, breeding pairs of laboratory rabbits and rodents that produce offspring which exhibit congenital conditions are culled. This may not always be the practice within commercial meat rabbit or small mammal breeder or hobbyist sectors. The increased longevity of companion rabbits and rodents and the diversity of animal source may alter the prevalence of certain conditions outside of research settings. Heart diseases of rabbits and rodents have received increasing attention as companion animal owners have come to expect similar care and treatment for their pet rabbits and rodents as for dogs and cats. As such, while similar small animal approaches may be used for diagnosis and treatment of conditions in rabbits and rodents, this remains an evolving area as more is learned about background cardiac conditions and diseases of each species.

Etiology

The etiology of most cardiac diseases of rabbits and small rodents is unknown, and the true prevalence of these conditions in the larger population of these animals is also unknown because of limited studies in this area. Cardiac conditions may be primary or secondary in nature in most species and may develop following intercurrent disease or due to nutritional deficiencies or excesses (e.g., vitamin D–related dystrophic calcification) or toxin or chemical exposures.

Aging studies in untreated mice and rats of different stocks and strains have provided an understanding of gross, histologic, and molecular cardiovascular changes that occur in the heart muscle of most mammals, including humans, during aging. Intrinsic, naturally occurring aging of the heart and cardiac myofibers is commonly seen in aging populations of laboratory mice and rats. As in humans, cardiac myofibers are seen to swell and decrease in number and interstitial fibrosis may develop, with accumulation of aging pigment and other proteins (e.g., lipofuscin and amyloid), which may cause the heart to stiffen over time. There are very few case reports of congenital malformations of the heart and cardiovascular system in rabbits and small rodents, likely because of fatal fetal or early postnatal outcomes.

More recently, several population or retrospective studies in wild rats and companion rabbits and guinea pigs have provided insight into naturally occurring cardiac conditions in these species outside of research settings. One study of cardiovascular conditions in wild black and brown urban rats in Canada indicated a moderate prevalence of cardiac lesions, including myocardial degeneration, inflammation, fibrosis, and/or myofiber mineralization in up to 33% of animals examined, with increased odds of lesions occurring in heavier, older, male black rats. In another retrospective review of medical records, 59 cases of cardiovascular disease were diagnosed in companion rabbits over an 18-year period, providing a prevalence of 2.6%. A similar retrospective study in guinea pigs suggested a cardiac disease prevalence of 2.8% (i.e., 80 affected guinea pigs over 11 years of records). In the rabbit study, cardiomyopathy, myocarditis, and valvular degeneration were more commonly diagnosed.

Predisposing Factors

In rabbits, guinea pigs, and other small rodents, the thoracic cavity is small compared to the size of the abdomen, and the heart occupies a higher percentage of space. Thus, any accumulation of fat (in obese animals), fluid (in animals with respiratory conditions), or masses (e.g., tumors) may increase the burden placed on the cardiovascular system of these animals and contribute to underlying degenerative changes. Similarly, increases in abdominal size due to bloat, gastric or intestinal dilatation or obstruction, and other conditions may result in significant mechanical impairment of heart function. Rabbits have poor collateral coronary artery circulation, which may predispose their myocardium to hypoxemia and subsequent ischemic damage, reinforcing the need for supplementary oxygen during injectable anesthesia.

Clinical Signs

Rabbits and rodents with underlying cardiac conditions may present with nonspecific signs of dyspnea, lethargy, cyanosis, and anorexia with or without concurrent weight loss. These animals may be very fragile and stressed, and may expire without warning, even when handled gently. The examination may need to be staged if the animal is demonstrating signs of distress, e.g., open-mouthed breathing, and animals can be lightly sedated and provided with oxygen by face mask or in a chamber, if needed.

Diagnosis

Thoracic auscultation using a pediatric stethoscope is challenging because of the small thoracic size and need for firm restraint in rabbits and small rodents. It may be very difficult to adequately ausculate a heart that normally beats at 200–300 bpm (rabbits) or up to 500 bpm for smaller species. Cardiac murmurs can be detected upon auscultation in some larger rabbits, but echocardiography, electrocardiography, and thoracic radiography are needed for definitive diagnosis of conditions in most animals. Clinical chemistry and hematology are necessary to follow the impact of

therapy and the presence of intercurrent disease or degenerative conditions.

Heart murmurs, arrythmias, increased heart size, valvular thickening or insufficiency, and pleural effusion may be detected in animals with congestive heart failure and valvular disease. Work-up of these cases proceeds as for other small animal species.

Treatment

There are no therapeutics specifically approved for treatment of cardiac diseases of rabbits, guinea pigs, and small rodents, and therapeutic approach will depend upon specific conditions diagnosed with extrapolation of treatments developed for cats and dogs. Clients should be advised that treatment is symptomatic only and directed toward improving the quality of life for the companion animal. As chronic renal disease is common in older rabbits, guinea pigs, and other small rodents, kidney function should be monitored closely with the use of diuretics and other medications cleared by the kidney.

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HEAT PROSTRATION

Hosts

All animals are susceptible to heat prostration or heat stroke, but adult rabbits, chinchillas, and guinea pigs are cold-adapted species and are particularly susceptible to increased ambient temperatures.

Etiology

High ambient temperatures alone or in combination with any of the predisposing factors listed below may lead to failure of thermoregulatory mechanisms and an increased body temperature beyond a level compatible with life.

Predisposing Factors

Predisposing factors to heat stroke include an ambient temperature greater than 28 °C (85 °F), high humidity (more than 70%), a thick hair coat, obesity, older age, pregnancy, direct sunlight, poor ventilation, insufficient or warm water, crowding, history of recent transportation by common carrier, confinement in a vehicle, transportation delay, adverse stress, and anxiety. Heat stroke victims, like food deprivation cases, may present without a complete history. This makes a thorough clinical examination essential.

Clinical Signs

Signs of heat stress include hyperemia of peripheral vessels in the extremities, rapid respiration, hyperthermia (rectal temperature above 41 °C [105 °F]), cyanosis, prostration, death, or unexplained mortality in otherwise healthy animals, especially groups of animals. Mortality is greatest in the uppermost cages in tiered row breeder settings because heat rises. There may be blood-tinged fluid in the nares and coming from the mouth. Food intake drops and water intake is increased greatly. Rodents have large salivary glands and respond to overheating by profuse salivation. Excess saliva escaping from the corners of the mouth is groomed over the face and sides with the forepaws, wetting the body and cooling the animal through evaporation.

Chronically heat-stressed rabbits eat and grow less, consume more water, and at temperatures of 32 °C (90 °F) and above for several days or even weeks, males become sterile. This is reversible if the ambient temperature returns to normal. Younger bucks 5–7 months of age are less susceptible to heat-induced sterility.

Necropsy Signs

Signs of heat stroke include hyperemia of tissues, particularly of the lungs and intestinal wall, and often dehydration and copious salivation.

Diagnosis

The history of acute onset in hot weather and the absence of evidence of ketosis or infectious or toxic disease support a diagnosis of heat stroke. Rodents with acute heat stroke or suffocation will have evidence of excessive salivation from the corners of the mouth. Fur may be wet and matted, and extremities (ears, tail, scrotum, and feet) may be hyperemic and cyanotic.

Treatment

Heat-stressed animals can be sprayed with water, carefully dipped into a cool bath (not an ice water bath), or wrapped in a dampened cloth until the rectal temperature returns to normal. Supportive care, for example, providing a warm, quiet comfortable environment with palatable food and water, and corticosteroids may be administered as well as IV or IO fluid therapy. The fluid bag can be put in ice water or the IV tubing can be run through ice water. Cool-water enemas can be tried for animals that will tolerate this treatment. Efforts to lower body temperature should be discontinued around 103 °F to preclude rebound hypothermia and shivering. Monitoring for acute renal failure or metabolic acidosis should be considered in select cases. The prognosis is usually guarded to poor, particularly if the body temperature has exceeded 41.1 °C (106 °F).

Prevention

Obese and heavily furred animals are particularly susceptible and should be conditioned to higher ambient temperatures, culled, or potentially groomed and given a haircut. Prevention of heat stress includes provision of shade; adequate air circulation, feed, and water; water sprays; or a container of ice placed in the cage.

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HELICOBACTER INFECTIONS

Hosts

Helicobacter spp. are important pathogens of laboratory animals, particularly rodents. *Helicobacter* spp. is the most common bacterial contaminant of research rodents in Europe and North America. Various *Helicobacter* spp. infect mice, rats, guinea pigs, rabbits, hamsters, gerbils, ferrets, dogs, cats, humans, and other animal species. There are no reports of *Helicobacter* spp. infections in chinchillas.

Etiology

Discovery of *Helicobacter hepaticus* occurred during an investigation into an unexpectedly high background incidence of hepatic tumors and hepatitis in control A/JCr mice in a carcinogenesis study. While infections with many *Helicobacter* spp. may be asymptomatic subclinical infection also may have profound systemic effects, confounding research. In one study, infection of mice with *Helicobacter* spp. resulted in altered gene expression in cecal tissues, prior to the onset of clinical signs in the mice, leading to upregulation of 25 genes and downregulation of three others. Colonization of the intestine in mice is dependent upon production of a cytolethal-distending toxin by the bacterium.

H. hepaticus and *Helicobacter bilus* are the two primary pathologic species in immunocompetent mice. Other species detected in mice include *H. muridarum, H. (Flexispira) rappini, H. rodentium*, and *H. typhlonicus*, and immunodeficient mice are susceptible to disease with some of these strains. These bacteria are microaerophilic, curved to spiral rods with variable numbers of flagella.

H. hepaticus and *H. bilis*, separately or in combination, are associated with a chronic typhlocolitis in immunodeficient mice. Confinement within the biliary system appears to afford protection against circulating antibody in chronically infected mice.

H. bilis has been reported to cause proliferative and ulcerative typhlocolitis and proctitis with rectal prolapse in nude rats. In addition to the hepatic lesions associated with *H. hepaticus* infections in immunocompetent and immunodeficient laboratory mice, wasting and chronic enterocolitis have been observed in immunocompromised mice and rats infected with *H. hepaticus, H. bilis, H. typhlonicus, H. rodentium*, or *H. muridarium.*

Spontaneous *Helicobacter* spp. infections have been reported in hamsters and gerbils. In one report in gerbils, attempts to rid the colony of *Helicobacter* spp. infection resulted in a *C. difficile* enterotoxemia. *Helicobacter* spp. infection is a classic example of chronic inflammation resulting in neoplasia induction. This model is used to reliably reproduce various gastrointestinal and hepatic tumors. Infection in hamsters with naturally occurring species may result in gastric adenocarcinoma and intestinal metaplasia.

Predisposing Factors

There is a strain-related variation in susceptibility to the disease. A/J, BALB/c, Swiss-Webster, and ICR mice are susceptible to typhlocolitis, while C57BL/6 mice are relatively resistant. An autoimmune component has been recognized in chronically infected mice with active hepatitis. There is a sex-based pattern of disease susceptibility to *H. hepaticus*, with male mice being more susceptible to hepatitis and females to enterocolitis.

Clinical Signs

Infection in mice may result in diarrhea, rectal prolapse, chronic weight loss, and anemia. Signs of cholangiohepatitis may be nonspecific.

Necropsy Signs

At necropsy, lesions may be present in both the small and large intestine, but they are usually most extensive in the large intestine. Chronic proliferative typhlitis, colitis, and proctitis with hyperplasia of mucosal epithelial cells, patchy disruption of the normal mucosal architecture, and mild mononuclear cell infiltration in the lamina propria are typical histologic findings in mice. In silver-stained sections of intestine, numerous spiral-shaped bacilli are evident within crypts and on the surface of the affected mucosa.

Infections with *H. hepaticus* in many immunocompetent strains of mice may result in chronic cholangiohepatitis, and in the immunocompromised host, chronic proliferative enteritis involving the cecum, colon, and rectum are possible sequelae. The typical findings in cases of hepatitis are focal necrosis with hepatocytomegaly, ductular cell hyperplasia, and pericholangitis. *Helicobacter* spp. infection may confound results of various experimental studies, particularly of those that use mice for inflammatory disease models. Hepatic tumors have been observed in A/J mice chronically infected with *H. hepaticus*. The bacteria are best demonstrated within bile canaliculi with the Steiner modification of the Warthin–Starry stain.

Transmission

Bacterial transmission is orofecal. Contaminated bedding is one possible source of infection. Chronic inapparent shedding is common. The organism may reside in the intestinal tract and in the bile canaliculi of the liver for months to years. Transplantable cell lines have been reported to be positive for *Helicobacter* spp. contamination, and all biologics should be ascertained to be free of infectious organisms prior to injection into live animals.

Diagnosis

Infections are typically diagnosed based on serology or histologic lesions, with confirmation of bacterial presence using silver or Giemsa stains. Culture of the bacterium is difficult and requires specific media and microaerophilic conditions, whereas PCR of fecal pellets is a rapid and sensitive test for the bacteria. For *H. bilis*, the most sensitive test for diagnosis is by PCR or culture of feces, regardless of mouse strain. Colony monitoring by serology alone may be challenging, as seroconversion to bacterial presence may take several weeks, assuming that infected animals are shedding sufficient numbers of bacteria in the feces.

Treatment

Helicobacter spp. was reported to be eradicated successfully in experimentally inoculated mice using a combination therapy that included metronidazole, tetracycline, and bismuth subcitrate. Other antibiotics that were tried with variable effectiveness included erythromycin and amoxicillin. Tetracycline, when used alone, was ineffective.

Prevention

Helicobacter spp. infections can largely be eliminated from colonies by cross-fostering pups within 48 hours of birth onto clean dams. Cesarean rederivation onto clean dams will also eliminate the bacteria. Traffic flow and personnel handling of animals should move from cleanest to dirtiest to minimize the possibility of colony contamination. Thought must be given to optimal husbandry practices on weekends, when reduced personnel are usually present. Shared equipment, for example, Morris water mazes, elevated plus mazes, and so forth, must be carefully cleaned between animals and between users with animals of differing health status.

Public Health Significance

H. hepaticus does not infect humans, although *H. pylori* (a human *Helicobacter* sp.) readily infects mice, gerbils, and guinea pigs and causes a severe gastritis.

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HEMATURIA AND PIGMENTED URINE

Hosts

Bloody urine or hematuria and urine otherwise pigmented are seen more commonly in rabbits than in rodents. Urine of adult rabbits is normally turbid with a yellow-brown tint and has an alkaline pH of approximately 8.2. Urine of young rabbits, which is more acidic, is free of precipitate. The urine first appears turbid or cloudy when young rabbits begin to eat green feed and grains. The turbid appearance of the urine is due to the abundance of crystal precipitate (some ammonium magnesium phosphate but mostly calcium carbonate) seen in normal alkaline urine. Crystals dissolve if the urine becomes acidic (pH 6–7), as is the case in adult rabbits with fasting, food deprivation, or inappetence. Guinea pigs and chinchillas also may produce urine with a turbid appearance due to calcium crystal excretion.

Etiology

In rabbits, if the urine contains blood, then uterine adenocarcinoma, urolithiasis, and cystitis are likely causes. Other less frequent causes are bladder polyps, pyelonephritis, renal infarcts, disseminated intravascular coagulation (DIC), leptospirosis, ruptured endometrial venous aneurysms, hemangiomatosis, and abortion. An intermittent benign asymptomatic hematuria has been reported in Lewis × Brown Norway rats due to intermittent rupture of hemorrhagic, papillary, proliferative masses in the renal pelvis. Infections due to *E. coli, Klebsiella* spp., *P. multocida, E. cuniculi*, and other bacterial, parasitic, or viral agents are possible causes of pyelonephritis. Plant toxicosis or trauma also can cause hematuria, and renal failure has been reported in guinea pigs following ingestion of oxalate-containing houseplants.

Some cases of red urine in rabbits are due to porphyrin-pigmented basic urine and urobilin from heme degradation. The intensity of the color is heightened by dehydration (usually because of water restriction) and excess dietary calcium. Calcium and magnesium are excreted principally in the urine of rabbits; however, calcium is excreted primarily in the bile of other mammals.

Chronic renal disease, although common, is unlikely to result in hematuria. Metastatic mineralization is not an uncommon cause of renal disease in guinea pigs over 1 year of age. Unthriftiness and muscle stiffness may result if soft tissues are similarly affected. This may result from feeding rabbit pellets to guinea pigs or from giving animals multivitamin supplements. To achieve adequate levels of vitamin C with these supplements vitamin D toxicosis is often created. Rabbits are also sensitive to vitamin D intoxication, and adults are more sensitive than younger animals. Clinical signs may be nonspecific and radiographic evidence of multiorgan mineralization may be diagnostic in some cases. Certain drugs may have nephrotoxic properties, particularly in dehydrated animals. Examples include gentamicin, tiletamine/zolazepam (Telazol®), and many NSAIDs.

Similarly, most rodent species are susceptible to a chronic degenerative renal disease that may be strain- or sex-specific, linked to ad libitum feeding or related to high protein levels or inappropriate protein formulations in the diet. This does not produce hematuria.

Predisposing Factors

Normal cloudy, yellow-tan tinted urine may appear darker if an animal is dehydrated. Cloudy red urine, commonly seen in apparently healthy rabbits, is often mistaken by inexperienced rabbit owners and caretakers as blood in the urine. Rabbits that are fed carrots and other fresh foods high in carotene are likely to exhibit more red pigment in the urine than are animals on lower carotene foods. A high calcium diet may promote urolithiasis.

Intact adult does have a high incidence of uterine adenocarcinoma. Discharge associated with this neoplasm may appear in the urine. The incidence of uterine adenocarcinoma is breed-specific and may be as high as 80% in the New Zealand white breed but is rarely reported in rex and Belgian breeds. The varieties of breeds seen in pet practice will include those

likely to develop this tumor. Predisposing factors for urolithiasis and cystitis include systemic or local bacterial, viral, or parasitic infections and dietary imbalances.

Clinical Signs

Animals with true bleeding episodes and hematuria may be clinically pale or anemic and show other signs associated with their primary disease, especially if the condition is chronic. Regardless of the specific etiology, hematuria is frequently the most prominent feature in clinical disease, whereas reddish pigment in the urine is observed commonly in non-clinical (nondiseased) cases.

Reproductive disturbances such as decreased fertility, small litter size, increased incidence of stillborn and retained fetuses, desertion of a litter, dystocias, and fetal resorption are clinical signs highly correlated with uterine adenocarcinoma in older female breeder rabbits. Nonspecific signs such as anorexia, loss of condition, and depression may be associated with either systemic or localized conditions such as urolithiasis with or without cystitis, pyelonephritis, toxicosis, or trauma.

Necropsy Signs

Gross lesions associated with hematuria depend on the cause. The uterus may be unilaterally or bilaterally enlarged with variations in color and have a nodular appearance in some cases. If endometrial hyperplasia is implicated, cystic ovaries are seen. If metastasis of an adenocarcinoma has occurred, gross nodular lesions may be found in any major organ including lungs, liver, and bone marrow. In endometrial hemangiomatosis, the uterine horns are enlarged and turgid, and, on cross-section, contain red-tinged watery fluid and a variable number of red-purple, firm, ovoid, and pedunculated masses. In cases of urolithiasis, concretions may be found anywhere in the bladder, urethra, ureter, or renal pelvis. Infection of rabbits with *E. cuniculi* may be apparent grossly in the kidneys as multiple, small, pale foci. Cystitis may be accompanied by gross changes in the bladder mucosa secondary to urine stasis.

Histologic lesions in uterine endometrial hyperplasia include proliferative changes of the endometrial glands and formation of papillary or polypoid cauliflower-like growths projecting from the luminal surface of the uterus. Uterine adenocarcinoma is characterized by anaplasia of the endometrial cells, proliferation of the endometrium with scattered mitotic figures, and a myxomatous appearance of the proliferating cells. The microscopic appearance of uterine hemangiomas includes congested and hemorrhagic polypoid nodules with laminated thrombi consisting of layers of fibrin and red cells in the vascular spaces. Microthrombi, hemorrhages, and cell necrosis may be seen in cases of DIC, whereas microabscesses and infarcts may be seen in systemic or local infections.

Diagnosis

Red urine from clinically ill animals with obvious signs of dehydration, bacterial infections, and other concurrent diseases or conditions can be differentiated from the urine of healthy animals by urinalysis, including urine cytology. Thorough physical examination, abdominal palpation, ultrasonography, radiography, ancillary blood tests (hemograms and serum chemistry for azotemia), and biopsy results are helpful in making a diagnosis. Culture and isolation of bacteria from a cystocentesis sample are useful in ruling out an infectious process.

Histopathologic examination of uterine tissue is essential to differentiate between benign uterine hyperplasia and the early stages of uterine adenocarcinoma. This facilitates an accurate prognosis so that therapeutic management may be prescribed.

Treatment

The treatment will depend on the inciting cause. Aggressive and prudent use of antibiotics, such as trimethoprim–sulfa or enrofloxacin, may be necessary to eliminate infection, and surgery may be indicated in cases of urolithiasis, uterine hyperplasia, and adenocarcinoma that has not metastasized. Rabbits with malignant neoplasia (e.g., uterine adenocarcinoma) have a poor prognosis once metastasis has occurred, at which time symptomatic treatment is at best palliative.

Prevention

Abundant fresh clean water should be provided ad libitum to prevent dehydration, and parenteral fluid replacement should be used in emergencies and life-threatening conditions. Neutering of pubescent females will prevent uterine tumor development in later years. Feeding a balanced diet, reduction of stress, and good husbandry practices are measures that may prevent some cases of hematuria.

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HEPATITIS E INFECTIONS IN RABBITS

Hepatitis E infections are considered an emerging disease in people and animals, and are an important cause of human hepatitis, especially in parts of Africa and Asia. There are at least

eight recognized genotypes that infect mammals, including newly identified genotypes in wild rats in Germany and farmed, feral, and companion rabbits in North America, Europe, China, and elsewhere. The virus can cross-infect between multiple species, and rabbits and rodents may serve as a reservoir for human infections. While hepatitis E infections are generally associated with acute, self-limiting signs, up to 20% mortality can be seen in pregnant women following acute infection.

Etiology

Hepatitis E is caused by small, nonenveloped RNA viruses in the Herpesvirus genus. In rabbits, both hepatic and intestinal replication of the virus occur, and the virus can be detected in the feces of actively infected and shedding animals. From the few surveillance studies that have examined natural infections in rabbits, the overall prevalence of infection appears low in farmed meat rabbits and very low in companion rabbits.

Predisposing Factors

No information is known about virus strain, or rabbit breed, or age susceptibility. It is also unknown whether pregnant does are more susceptible to serious consequences following acute infection, as pregnant women are.

Clinical Signs

Following acute infection, naïve animals may die peracutely with no premonitory signs. In enzootically infected rabbit herds no clinical signs may be noted. Clinical signs may be augmented with co-infections with other bacteria or viruses inducing debilitation.

Necropsy Signs

In experimental studies and in the few reported cases of natural infection hepatomegaly may be seen in rabbits during the acute phase of the disease.

Diagnosis

There are currently no commercial diagnostic assays available for this virus. Affected animals may demonstrate increased serum levels of ALT. Assays may be available at some research labs or diagnostic pathology centers.

Treatment

There is no specific treatment for rabbits. As per other viral infections, supportive care can be given to rabbits who go off feed.

Prevention

Transmission of hepatitis E viruses occurs by fecal–oral and bloodborne routes. Most needles used for treatment of rabbits are intended to be single use and disposable. Good hygiene of cages and pens and eliminating needle re-use may help to reduce opportunities for transmission. Good handwashing practices before and after handling rabbits is important to prevent transmission of the virus to human caregivers or to other animal species, such as pigs. Additionally, minimizing opportunities for domestic animals to contact feral or wild rabbits will help to prevent transmission between animals.

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HERPESVIRUS INFECTIONS OF RABBITS

A rabbit-specific herpesvirus, leporid-herpesvirus-4 (LeHV4), was first described in companion and meat rabbits in Alaska in 2008. Subsequently, spontaneous cases of LeHV4 have been identified in companion rabbits in Canada and in parts of the US. Although human herpes simplex virus (human herpesvirus-1) infection-associated encephalitis has been reported in rabbits sporadically, this new domestic rabbit-specific herpesvirus presents with different signs.

Etiology

Alphaherpesvirus infections in rabbits are rare, and domestic or European rabbits are not susceptible to herpesvirus infections of wild, cottontail rabbits (i.e., LeHV1, LeHV3, and others). Rare and spontaneous novel alphaherpesvirus disease outbreaks have been reported in outdoor-housed meat and companion rabbits in the US and Canada.

Predisposing Factors

No information is known about virus strain, or rabbit breed or age susceptibility.

Clinical Signs

Viral infection induces a severe necrotizing bronchopneumonia and animals may present with pyrexia, anorexia, conjunctivitis, facial swelling and crusted lesions, lethargy, respiratory distress (including the presence of frank blood from the nose secondary to upper respiratory tract ulceration), and abortion. Animals may die suddenly following a stressor, such as veterinary examination.

Necropsy Signs

Gross lesions may include ulcerative facial dermatitis and rhinitis, a severe, acute hemorrhagic bronchopneumonia, and splenic enlargement and congestion. On tissue section, pulmonary lesions may include a generalized necrotizing and hemorrhagic bronchopneumonia with denuding of airways, flooding of alveoli with edema fluid and fibrinous exudates, mixed neutrophilic and mononuclear cell infiltrates, and fibrinoid necrosis and thrombosis of arterioles. Coalescing fibrinohemorrhagic splenic necrosis and focal hepatic necrosis also may be present microscopically. In sections of skin, lung, and spleen, numerous multinucleated syncytial cells with pale eosinophilic (pink) intranuclear inclusion bodies may be scattered throughout the cells undergoing degeneration (Figure 5.13).

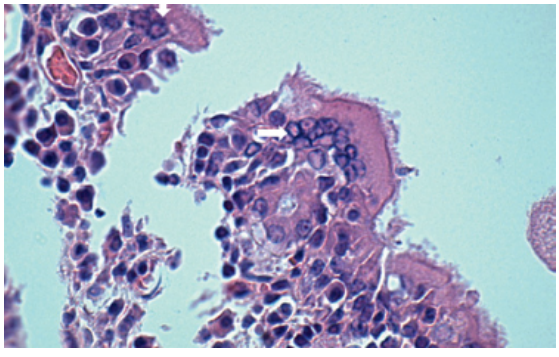


FIGURE 5.13. Image of ciliated nasal epithelial cells from a rabbit infected with leporid herpesvirus-4. Some clusters of infected cells are seen to contain a glassy pink intranuclear inclusion body (arrows) characteristic of herpesvirus infections.

Diagnosis

The combination of pulmonary, splenic, nasal, and skin lesions with the presence of glassy eosinophilic intranuclear inclusion bodies is pathognomonic for LeHV4 infection. However, experimental studies have suggested that intranuclear inclusion bodies are only present in tissues briefly during the course of the disease. Further, sections of nasal turbinates are infrequently evaluated during routine microscopic analyses at diagnostic laboratories. Otherwise, there are currently no commercial diagnostic assays available for this virus. Assays may be available at some research labs or diagnostic pathology centers. For a definitive diagnosis, testing or sequencing should distinguish between human versus rabbit variants of herpesviruses. Virus isolation and PCR assays can be performed on nasal secretions during active infection. Use of PCR analyses decrease biohazard risk and PCR amplification also is effective on frozen and formalin-fixed paraffin-embedded tissues.

Differential diagnoses include rabbit hemorrhagic disease virus (RHDV, see further in Chapter 5) infection, *P. multocida*—induced bronchopneumonia, sepsis, shock, adverse drug reactions, and immune-mediated disease. Human alphaherpesvirus infections present almost exclusively as encephalitis.

Treatment

There is no specific treatment for rabbits. As per other viral infections, nonpharmacologic supportive care can be given to rabbits who go off feed. In both natural and experimentally induced cases of LeHV-4, some of the rabbits provided with supportive care survived the acute phase of infection and disease.

Prevention

While the risk of LHV4 infection in laboratory rabbits is unknown, the prevalence of infection is very low. The few reported spontaneous cases have arisen in rabbits with access

to the outdoors. While it is possible that the virus may have been transferred from wildlife, possibly through insect vectors, it seems more likely that the virus may have arisen as a variant of a primate virus that was passed through humans. More sequencing data is needed to better understand the phylogenetic origins of LeHV4.

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HYPOVITAMINOSIS C (SCURVY) IN GUINEA PIGS

Hosts

Guinea pigs and primates, including humans, are among a small number of animal species with an absolute requirement for dietary or exogenous L-ascorbic acid or vitamin C, a vitamin active in certain biologic oxidation and reduction systems. Other animals that require vitamin C are a few species of fruit-eating bats, channel catfish, and certain birds, such as the red-vented bulbul. Although closely related to guinea pigs, chinchillas are able to synthesize enough vitamin C to meet their daily needs and are not susceptible to scurvy.

Etiology

The expression of the hepatic microsomal enzyme L-gulonolactone oxidase is genetically controlled. Guinea pigs, primates, and the other species that normally require ascorbic acid in their diet lack the gene necessary to produce the oxidase, which is one of several enzymes involved in the conversion of L-gulonolactone to L-ascorbic acid. Ascorbic acid is essential in the hydroxylase reactions necessary for formation and cross-linking of hydroxyproline and hydroxylysine in collagen and in the metabolism of cholesterol to bile acids, amino acids, and carbohydrates. A deficiency leads to fragmentation of collagen and intercellular ground substance. Because vitamin C is water-soluble, there is no internal storage depot and guinea pigs require vitamin C daily.

Predisposing Factors

Age, sex, diet, pregnancy, lactation, concomitant disease, and environmental conditions all affect the duration of onset and the magnitude of signs seen with ascorbic acid deficiency. Young guinea pigs show signs of deficiency within 2 weeks or less if vitamin C is withheld completely. Guinea pigs up to 6 weeks of age catabolize vitamin C much faster than those older than 4 months, and some animals may show individual adaptations to dietary levels of vitamin C.

Ascorbic acid content of feed is reduced by dampness, light, heat, and prolonged storage. Up to 50% of vitamin C activity in stored feed is lost within 6 weeks. Similarly, up to 50% of vitamin C activity is lost within 24 hours when in water, such as in an open crock or bowl.

Clinical Signs

Pet or research guinea pigs with scurvy are lethargic, weak, anorexic, and often found hunched or lying in the cage. Many exhibit a characteristic "bunny-hopping" gait due to inability to extend their stifle joints. They may vocalize or bite due to pain when restrained and often have enlarged limb joints and costochondral junctions, a rough hair coat, diarrhea, weight loss, bruising, and conjunctival and nasal discharge (Figures 5.14 and 5.15). Animals may grind their teeth and salivate excessively, and opportunistic infections are common. Young, growing animals are more susceptible to bone deformities and neurodevelopmental anomalies than are older animals. A combined deficiency of vitamins E and C may produce signs of paralysis and death, related to concurrent spinal cord and brain degeneration.



FIGURE 5.14. Conjunctivitis and nasal discharge in a guinea pig with hypovitaminosis C.



FIGURE 5.15. The nasal discharge has been transferred to the forepaws of this animal with hypovitaminosis C during grooming.

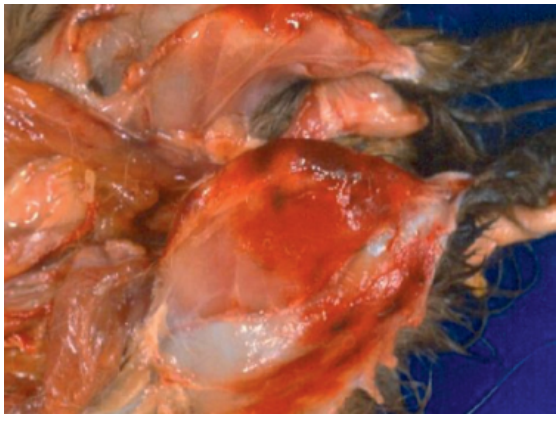


FIGURE 5.16. Stifle joint of a guinea pig with hypovitaminosis C, demonstrating periarticular edema and hemorrhage.

Differential diagnoses for lameness, diarrhea, upper respiratory tract disease, or anorexia in guinea pigs should always include consideration of hypovitaminosis C among possible causes. Parenteral vitamin C supplementation should be part of the therapeutic regimen for any sick or anorexic guinea pig.

Necropsy Signs

Gross lesions of scurvy are related to abnormalities of bones, cartilage, and blood vessels. Signs, most prominent in growing animals, include hemorrhage into the subperiosteum, subcutaneous and periarticular tissues, skeletal muscle and intestine, and separation at the epidiaphyseal junction (Figures 5.16 and 5.17). Adrenal glands are usually markedly enlarged.

The consequences of aberrant synthesis of collagen cement substance and connective tissue are evident microscopically, most notably in young animals. Persistence of epiphyseal cartilage with impaired ossification (scorbutic lattice), microfractures, and subperiosteal hemorrhage are common features. In the absence of new bone formation, the calcified cartilage lattice is thickened and relatively susceptible to mechanical forces, resulting in microfractures and hemorrhage. Proliferation of poorly differentiated fusiform mesenchymal cells is seen in affected areas (periosteal and periarticular tissues). Endothelial junctional defects in skeletal muscle lead to hemorrhage and fragmentation of myofilaments. Scurvy leads to decreased macrophage migration and decreased phagocytic activity of neutrophils. Gross and histologic lesions may be more subtle in older guinea pigs.

Diagnosis

A thorough dietary history and observation of clinical signs, particularly joint stiffness, provide a tentative diagnosis. Many pet guinea pig owners believe they are providing adequate vitamin C by feeding the appropriate pellets,



FIGURE 5.17. Hemorrhage and edema along the costochondral junctions of a guinea pig with hypovitaminosis C.

supplementing with multivitamins in the water, and feeding fresh fruits and vegetables. They may not be aware that stored guinea pig pellets lose up to 50% of vitamin C activity rapidly, small mammal multivitamin supplements do not contain sufficient vitamin C for guinea pigs, and the vitamin C content of fresh fruits and vegetables varies greatly; for example, one medium-size carrot contains only 4 mg, and the vitamin C content of iceberg lettuce is negligible (Table 5.2).

Necropsy findings, such as periarticular hemorrhage and enlarged costochondral junctions, further support the diagnosis. Marginal deficiencies, especially in adults, and early cases often are difficult to diagnose from the nonspecific signs of weakness and anorexia. Secondary bacterial or metabolic diseases may obscure subtle signs of vitamin C deficiency. Subclinical vitamin C deficiency should be suspected with any ill guinea pig.

Table 5.2. Vitamin C content of some fruits and vegetables.

Fruit/vegetable	Amount	Vitamin C content (mg)
Apple, w/skin	1 medium	8
Apricots	3 medium	11
Banana	1 medium	10
Blackberries	1/2 cup	16
Blueberries	1/2 cup	7
Cantaloupe	1/2 cup	31
Grapefruit	1/2 medium	38
Guava	1 medium	165
Honeydew melon	1/2 cup	16
Kiwifruit	1 medium	70
Mango	1/2 medium	29
Nectarine	1 medium	7
Orange	1 medium	70
Papaya	1/2 cup	46
Peach	1 medium	6
Pear	1 medium	7
Pineapple	1/2 cup	46
Raspberries	1/2 cup	17
Strawberries	7	49
Mandarin orange	1 medium	22
Broccoli	1/2 cup	41
Cabbage, green	1/2 cup	12
Carrot	1 medium	4
Cauliflower	1/2 cup	25
Celery	1 stalk	1
Cucumber	4 slices	1
Lettuce, iceberg	1 cup	2
Lettuce, romaine	1 cup	14
Parsley	100 g	133
Peas, snowpeas	10	20
Pepper, green	1/2 medium	66
Pepper, red	1/2 medium	113
Pepper, yellow	1/2 medium	171
Tomato, red	1 small	16

Adapted from Nutrient Content of Some Common Foods, Health Canada, Ottawa, 2016.

Treatment

Active ascorbic acid supplied daily, or at least every third day, via feed, water, or parenteral injection at 5–10 mg/kg body weight for maintenance or 30 mg/kg during pregnancy or 25–50 mg/kg during deficiency will frequently reverse the consequences of a deficiency. Clinical recovery usually requires around 1 week of therapy and may not be complete. Malocclusion due to microfractures of the mandible is a possible sequela. If the abrupt change in the taste of the feed or water causes the guinea pig to refuse the diet or to drink, then giving ascorbic acid directly per os may be necessary. Multivitamins should not be used because of the potential for toxic overdose of vitamins other than C.

Any sick guinea pig should be treated with daily vitamin C, preferably by the parenteral route. The benefits of empirically administering vitamin C vastly outweigh any risk associated with repeated injections.

Prevention

Provision of adequate, fresh, stabilized vitamin C in feed or water at recommended daily levels (200 mg/L in the drinking water) will prevent hypovitaminosis C. The instability of the vitamin–water solution, as well as the presence of chlorine in water, warrants daily vitamin–water changes. Metal, hard water, and heat also cause accelerated deterioration of ascorbic acid in solution. L-ascorbic-2-polyphosphate is more stable against oxidation or hydrolysis in neutral or alkaline solutions. Commercial guinea pig feeds contain approximately 800 mg/kg diet of vitamin C when milled. To ensure adequate vitamin C, feed should be stored at less than 22 °C and be used within 90 days of milling, although many guinea pig diets now contain a stabilized potentiated form of vitamin C and have a 6-month shelf life. Supplements containing 25 mg vitamin C are available for guinea pigs (Natural Science Vitamin C Support, Oxbow®, http://www.oxbowanimalhealth.com) or human orange-flavored supplements (broken into halves or quarters) can be used to provide the daily requirement. Many guinea pigs regard these tablets as a tasty treat and eagerly take them from the hand, or the tablet can be pushed into the side of the mouth behind the fleshy cheek invaginations, where it is chewed and swallowed.

Adequate daily ascorbic acid is contained in a quarter orange, a half-handful of parsley, or in a few pieces of sweet red or yellow pepper. The vitamin C content of other fruits and vegetables is listed in Table 5.2. Kale, broccoli, cabbage, brussels sprouts, and other members of the Brassica family are relatively high in vitamin C but also result in gas production, so should be fed only in very small amounts to avoid bloat. Cabbage also contains potentially goitrogenic and estrogenic substances.

The water-soluble nature of vitamin C makes overdose very unlikely if animals are well hydrated, so any combination of the above forms of supplementation may be used safely. Any excess ascorbic acid is eliminated in the urine.

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LAWSONIA INFECTIONS (PROLIFERATIVE ILEITIS/ENTEROPATHY)

Hosts

Young Syrian hamsters are highly susceptible to proliferative ileitis caused by infection with *L. intracellularis*. Infections may occur when they are either naturally or experimentally inoculated per os with intestinal or fecal material from affected animals. Rabbits, as well as some strains of mice, ferrets, and pigs, are also susceptible to infection and disease with this agent.

Etiology

L. intracellularis is an obligate, intracellular nonmotile, Gram-negative, and agyrophilic organism occurring as curved to straight short rods. Depending upon the circumstances and the species affected, the clinical presentation may vary from an acute onset of profuse diarrhea and dehydration with high mortality (regional ileitis in hamsters) to an asymptomatic carrier state, to animals with chronic diarrhea, weight loss, and variable mortality (e.g., proliferative enteropathy in rabbits). Proliferative ileitis is a convenient name for the disease because both hyperplastic and inflammatory components are included. Alternative names in hamsters are "wet tail" and "transmissible ileal hyperplasia."

Changes associated with this disease are likely to have a significant effect on intestinal absorption of water and nutrients. In a study of changes in intestinal absorption in infected rabbits, abnormalities noted included decreased basal intestinal water, sodium, chloride, and glucose absorption; and elevated basal adenylate cyclase activity.

In addition to intestinal disease associated with primary infections with this organism, cases of proliferative enteropathy associated with a dual infection of *L. intracellularis* and an enteropathogenic strain of *E. coli* have been documented in hamsters. Similar cases of dual infections are seen frequently in commercial rabbitries.

Transmission

The bacterium is passed from weanling to weanling or from adult to weanling by the fecal–oral route. Although there is some subspecies host adaptation, the bacterium may readily be transmitted between pigs and rabbits, and rabbits and calves.

Predisposing Factors

Recently weaned hamsters (3–6 weeks of age) are most often affected clinically. Improper diet, intercurrent disease, exposure to infected animals, primiparous litters, crowding, dietary changes, and shipping predispose to development of the disease.

Clinical Signs

Proliferative ileitis has both acute and subacute clinical consequences. The acute condition involves lethargy, matted hair coat, hunched posture, anorexia, irritability, watery diarrhea, emaciation, and death within 48 hours. In subacute cases, survivors do not gain weight and may die at any time from ileal obstruction, intussusception, peritonitis, or impaction. Hamsters with intussusceptions may have bloody diarrhea and a prolapsed rectum and colon.

Necropsy Signs

Lesions of *L. intracellularis* infection are usually most extensive in the terminal small intestine. Typical changes are those of proliferative ileitis, with increased mitotic activity of crypt epithelium, and lymphohistiocytic cell infiltration into the lamina propria. Blunting and fusion of adjacent villi, dilatation of lacteals, and marked distortion of the normal architecture are seen in advanced cases.

Diagnosis

Diagnosis of proliferative ileitis is based on the clinical observation of diarrhea ("wet tail") and on the enlarged, thickened, and corrugated appearance of the distal small intestine in weanling hamsters and young mice and rabbits. Young hamsters often have enteritis without ileal proliferation. In Steiner or Warthin–Starry silver-stained sections of affected ileum, large numbers of bacilli are often aligned within the apical cytoplasm of enterocytes, with sparing of the microvillous border. The bacterium has stringent growth requirements and cannot be cultured in cell-free media because of a metabolic requirement for preformed mitochondrial triphosphate energy sources. A commercial tissue PCR test for bacterium identification in the ileum is available in some labs.

In rabbits, the disease is often mild and may be an incidental finding at necropsy. In mice, the bacterium predominantly affects the cecum, with similar proliferative and inflammatory changes, as described for hamsters.

Treatment

Treatment includes supportive fluids (oral or parenteral electrolytes or lactated Ringer's solution) for dehydration, an antidiarrheal, such as bismuth subsalicylate, up to 2 mL PO, and appropriate antibiotics such as tetracycline, enrofloxacin, metronidazole, or trimethoprim–sulfa, which can be administered orally or via the drinking water. Despite treatment, many animals will die of this disease.

Prevention

Affected animals should be isolated to prevent transmission of the disease, and cages and the environment should be thoroughly disinfected. Otherwise, high husbandry standards, frequent bedding changes, absence of environmental stressors, and use of cage filter lids may reduce the transmission of the bacterium within a colony or facility.

Public Health Significance

Proliferative ileitis is not known to be transmissible to humans.

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LISTERIOSIS

Hosts

Listeriosis is most commonly detected in conventionally raised rabbits and chinchillas, where it generally causes sporadic deaths or limited epizootics, particularly in pregnant animals.

Etiology

Listeria monocytogenes is a Gram-positive, motile nonspore-forming rod that is capable of growing at cold temperatures.

Predisposing Factors

Animals in advanced pregnancy are more frequently clinically affected, probably because the pregnant uterus and placenta present the most favorable environment for growth of the organism. Listeriosis in nonpregnant animals is often associated with predisposing factors (e.g., experimental manipulations) that may impair the normal immune response.

Transmission

The bacterium may be introduced into a herd via infected animals, by contact with a contaminated environment, or through contaminated feed. Feed may become contaminated because of inappropriate storage or processing methods, or hay may be contaminated in the field by wild rodents prior to processing. The method of transmission is fecal–oral. Equipment, cages, feed, and water contaminated with infected feces are the most important factors involved in the spread of the disease to other animals within the herd.

Clinical Signs

Affected animals may show signs of anorexia, lethargy, bruxism, and slow wasting. Animals more commonly present with constipation because of dehydration and reduced food intake, and rectal prolapse may occur. Central nervous signs such as blindness, head tilt, or convulsions may occur rarely in advanced cases. In pregnant animals, late-term abortions are seen. A high mortality rate is common in affected animals.

Necropsy Signs

In affected animals, there is often focal hepatic and splenic necrosis, lymphadenopathy, ecchymoses, acute metritis, hydrothorax, ascites, and anasarca. Histologically, there are foci of coagulation necrosis in the liver, with neutrophilic infiltrates. In animals that succumb during the perinatal period, acute suppurative metritis and placentitis may be observed.

Diagnosis

A presumptive diagnosis may be made from the history and gross findings. The organism is readily cultured from affected tissues using cold enrichment techniques.

Treatment

In other species, including humans, oral penicillins are the drugs of choice for treating listeriosis. These should not be used in rabbits and chinchillas because of the concern for antibiotic toxicity. Tetracycline has been used to effectively treat animals;

however, treatment must be initiated early in the course of the disease to be curative. Thorough cleaning and disinfection of caging and other equipment is needed following diagnosis of listeriosis. *L. monocytogenes* is susceptible to many common disinfectants including sodium hypochlorite, povidone iodine, chlorhexidine, 70% ethanol, and quaternary ammonium agents. Disinfection efficacy can be influenced by the presence of organic matter and adherence of the organism to surfaces.

Prevention

Purchase of animals from clean breeding colonies is important for preventing this condition. In addition, high sanitation standards for equipment, water bottles, and pens will minimize transmission. Dust baths should be changed frequently and shouldn't be shared between cages of chinchillas. Any sick animal should be isolated from healthy ones and appropriate hand-washing regimes should be followed before and after handling sick animals. All food should be stored properly to minimize contamination by vermin. Hay can be autoclaved before feeding to kill any bacteria present.

Public Health Significance

L. monocytogenes can cause disease in humans which can be very serious in pregnant women, people over 65 and those with weakened immune systems. The public health aspect is an important consideration when determining whether to treat or euthanize an animal, because treatment may not preclude a long-term carrier state. The organism may be harbored as an inapparent infection in various species.

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LIVER LOBE TORSION IN RABBITS

Liver lobe torsion is a sporadic condition diagnosed in companion rabbits and no preexisting conditions or tendencies have been identified. Animals with torsions may present with nonspecific signs, including anorexia, lethargy, and decreased fecal output or may die suddenly. Clinical chemistry changes may include anemia, thrombocytopenia, elevations of ALT, AST, and ALP. Abdominal radiography is less helpful, but abdominal ultrasonography may demonstrate abnormalities in hepatic blood flow, shape, size and echogenicity. The caudate lobe is most frequently affected and surgical lobectomy is curative.

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LYMPHOCYTIC CHORIOMENINGITIS VIRUS INFECTION

Hosts

The natural reservoir host for the lymphocytic choriomeningitis virus (LCMV) is the wild mouse, in which the prevalence of infection varies and may approach 100% in some regions. Natural infections occur in mice, guinea pigs, man, monkeys, and wild mice (*Apodemus sylvaticus*). A variety of other species can be infected experimentally. Infection can be transmitted readily to hamsters, which were the source of several hundred cases of lymphocytic choriomeningitis in humans in the United States in the 1970s. More recently, the virus resulted in the deaths of numerous individuals in the United States and France who received organ transplants from an infected individual in whom the infection had not been recognized or screened for. Since a 2005 US outbreak, significant measures have been taken to eliminate the infection from small mammal pets distributed and sold in pet stores across the United States. Transplantable tumors of mice, hamsters, and guinea pigs; tissue culture cell lines; and virus and protozoan stocks may become persistently contaminated with LCMV and act as a source of virus to inoculated animals.

Etiology

LCMV is an enveloped arenavirus (RNA). On the basis of clinical signs, viscerotropic and neurotropic strains exist. The virus is widespread in Europe and the Americas and is rare in laboratory mice, but common in wild mice, which are presumed to be the natural host of the virus. Hamsters pose a serious risk because they develop persistent infections following natural exposure as adults, unlike mice. Rats are not naturally susceptible.

Transmission

In utero transmission is common in an infected mouse population, but bite wounds may be a more common route of transmission in hamsters. The virus is passed in the urine, saliva, milk, and feces and enters susceptible individuals via traumatized skin, the conjunctiva, or respiratory passages. Blood-sucking arthropod vectors, such as ticks, lice, and mosquitoes, as well as dust or other fomites, may be transmission vehicles. Animals infected prenatally shed the virus for approximately 9 months, whereas animals infected postnatally shed the virus for 2–3 months. Mice have been accidentally infected by the inoculation of LCMV-contaminated transplantable murine tumors.

Predisposing Factors

Factors that predispose to the entry or persistence of LCMV infection in a colony include wild rodent invasion; introduction of carrier animals; use of infected tumors, cell lines, and other biologic products; decreased host resistance; and cutaneous traumatization.

Clinical Signs

The clinical signs of lymphocytic choriomeningitis are almost always subclinical but depend on the host's resistance and age when infected, although the various categories of the disease are not always delineated. If mice are exposed in utero or as neonates, they develop immunologic tolerance, allowing persistence and chronic shedding. Tolerance eventually breaks down later in life with lymphocytic infiltration of multiple organs and antigen–antibody complex glomerulonephritis. Adoptive transfer of T cells from immune mice to subclinically infected mice leads to clinical disease (lymphocytic chorio meningitis) and death. Virus strains are classified as "docile" or "aggressive" and "viscerotropic" and "neurotropic" for experimental purposes. Neonates survive when inoculated intracerebrally because their immune system is immature and no inflammatory reaction results. Adult mice inoculated intracerebrally die. These two experiments are used as bioassays for the virus.

Signs of acute infection in mice continue for 1 or 2 weeks and include decreased growth, rough hair coat, hunched posture, blepharitis, weakness, photophobia, tremors, and convulsions. The terminal stage of a persistent tolerant infection, which occurs over several weeks in 5- to 12-month-old mice, is characterized by weight loss, blepharitis, impaired reproductive performance, and runted litters.

Necropsy Signs

There are minimal gross signs of infection. Visceral organs, including the liver, kidneys, lungs, pancreas, blood vessels, and meninges, are infiltrated by lymphocytes and there may be moderate to marked necrosis of lymphoid follicles in multiple organs. A glomerulonephritis of probable immune complex origin is a characteristic feature of terminal persistent tolerant infection. Pituitary dwarfism has been produced in newborn mice inoculated with LCMV.

Diagnosis

Except for cases of persistent tolerant infection, infected animals either die or develop circulating antibodies, which can be detected serologically by neutralizing antibody, IFA, or ELISA techniques. MAP tests or PCR-based screening tests may be useful in screening suspect tumors and other biologic materials for LCMV. Because infections are asymptomatic with nonspecific clinical signs, virus isolation, and serology are preferred diagnostic procedures.

Prevention

Screening diagnostic tests are methods for monitoring and maintaining an LCMV-free colony. Filter cage covers reduce aerosol transmission, and the exclusion of insect and wild rodent vectors from the colony prevents introduction of the virus. The potential for vertical or transuterine passage of the LCMV complicates eradication.

Public Health Significance

Lymphocytic choriomeningitis may be transmitted from infected animals to humans through direct or indirect contact with feces or urine or via infected murine tissues. LCMV is also transmitted by biting. Humans are typically exposed to the virus when bitten by pets or by contact with contaminated urine (ingestion, inhalation, dermal contact). In immunocompetent individuals, the disease may be asymptomatic or associated with mild flu-like disease; however, fatalities have been reported in immunocompromised individuals following exposure. The bacterium has been transmitted by subclinically infected donors to human organ recipients with fatal consequences. Care must be taken in handling, bleeding, or processing tissues from suspect infected animals.

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MALOCCLUSION AND DENTAL DISEASE

Hosts

Dental disease is the most common clinical condition seen in small mammal pets (see Chapter 3). Malocclusion is seen commonly in the incisors (maxillary brachygnathism) and cheek teeth of rabbits, guinea pigs, and chinchillas. Overgrowth of incisors is occasionally seen in rats, mice, hamsters, and gerbils.

Etiology and Predisposing Factors

Both rabbits and rodents are monophyodont, with one set of dentition throughout life. The incisors of rabbits and rodents are elodont and grow throughout life, as do the cheek teeth of chinchillas, guinea pigs, and rabbits. For both rabbits and rodents, the incisors grow at a rapid rate of approximately 55–100 mm/yr. Malocclusion and tooth overgrowth result when, for genetic, dietary, infectious (abscesses), or traumatic reasons, elodont teeth do not occlude properly and therefore do not wear normally. Loss or malalignment of all or part of a tooth usually leads to overgrowth of the opposing tooth. Teeth that are dead because of infected crowns are usually discolored.

In the rabbit, incisor overgrowth can create a condition known as "buck teeth." The underlying cause of this malocclusion in the rabbit is an autosomal recessive trait that results in an abnormally short skull, in the region of the maxillary diastema, relative to the length of the normal longer mandible. Incisor overgrowth is more common in dwarf breeds.

Overgrowth of elodont cheek teeth is the most common dental problem of companion rabbits. Dental lesions including clinical and reserve crown elongations, buccal or lingual spurs, dentin hypoplasia, increased curvature of the teeth, periodontal disease, and odontogenic abscesses are also common. Dental disease is likely indicative of dietary mismanagement, including hypovitaminosis D in indoor-housed companion rabbits, as well as predisposing genetic factors. Commercial diets, although convenient to feed, do not promote normal chewing patterns seen with less energy-dense and more abrasive grasses consumed by wild rabbits. Dental diseases may also lead to signs involving other organs such as retroorbital abscesses, dacryocystitis and conjunctivitis, dermatitis from a lack of grooming or ptyalism, odontogenic rhinitis, and hematogenous spread of bacteria causing thoracic or abdominal abscesses.

Malocclusion in guinea pigs is most conspicuous in the most rostral cheek teeth, but all cheek teeth are usually uniformly affected (Figure 5.18). The condition is difficult to detect because of the abundance of loose skin in the edentulous diastema. The condition may be linked to a history of intermittent periods of poor nutrition, for example, vitamin C deficiency, or it may have a genetic basis, which can result in narrowing of the gap between mandibles. In guinea pigs, the lower cheek teeth overgrow in a lingual direction, which, in part, pins the tongue to the floor of the mouth and results in difficulty in food prehension and swallowing. The upper cheek teeth overgrow laterally and sharp points that develop on these teeth will lacerate the buccal mucosa.

Parvovirus infections may cause epidemic incisor loss with high mortality in suckling and weanling hamsters.

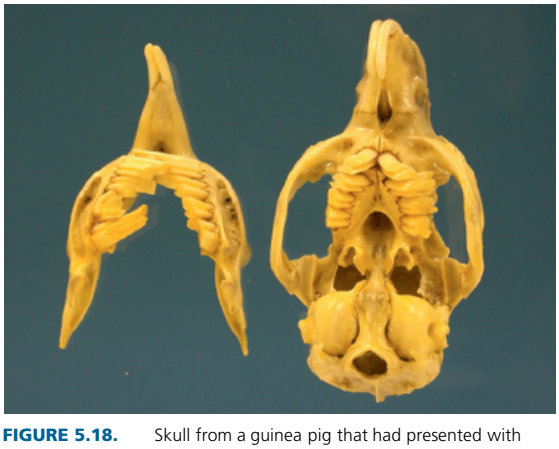


FIGURE 5.18. Skull from a guinea pig that had presented with anorexia. There is overgrowth of the upper (R) and lower incisors (L) as well as the cheek teeth. Overgrowth of the lower cheek teeth had resulted in tongue entrapment.

Clinical Signs

Overgrown teeth result in trauma to the inner cheeks, tongue, and mouth, which may cause dysphagia, ptyalism (slobbering), blood in the cage, anorexia, weight loss, starvation, and eventually death. The drooling around the mouth and onto the forequarters predisposes to moist dermatitis. Malocclusion is a common cause of chronic weight loss in rabbits and rodents, especially guinea pigs and chinchillas. For this reason, inspection of the mouth is an essential component of the physical examination. Signs related to other organ system are also commonly encountered such as dyspnea and nasal discharge, epiphora and conjunctivitis, unkempt fur coat, and mandibular abscesses.

The most rostral cheek teeth in guinea pigs can be assessed for overgrowth by inserting the pinky finger into the diastema, pressing it firmly onto the teeth, withdrawing the finger, and examining the width between the depressions made in the skin. Anesthesia and endoscopic examination (stomatoscopy) combined with skull imaging is usually required for a complete evaluation, and sharp points and lingual and buccal lacerations must be actively sought. The close apposition of the cheeks to the upper arcades precludes visual inspection in all but the largest rabbits.

Treatment

Dental equipment designed specifically for rabbits and rodents, such as specula and cheek dilators, are readily available from veterinary suppliers. Use of nail trimmers, side-cutters, or other types of clippers is not appropriate as they may crack or split the teeth longitudinally, leading to pulp exposure, pain, and abscessation.

Recognition of the normal length and appearance of rabbit and rodent incisors is critical to avoid unnecessary trimming, which could harm the animal. In particular, the lower incisors of guinea pigs and hamsters often appear overgrown to the uninitiated. In addition, the intermandibular joint of hamsters, rats, and mice is somewhat flexible and allows the lower incisors to mildly splay apart, which should not be misinterpreted as a fracture. Treatment of incisor overgrowth involves repeated filing or use of a dental burr in a low-speed dental handpiece. In very severe cases, extraction of all the incisors may be necessary to preclude retrimming visits every 4–6 weeks.

Access to the cheek teeth is more difficult and animals must be anesthetized and care taken to guard against trauma to the cheeks, gums, and tongue while performing dental work. Use of an appropriately sized speculum and cheek dilators can greatly assist in the examination. An adjustable table-top dental positioner for rabbits is available, which greatly facilitates examination and access. An otoscope or nasal speculum with light source and a narrow tongue depressor may also be helpful. Cheek tooth elongation can be corrected by using a rotating tool with a diamond-coated burr. Alternatively, molar cutters, rasps, or a flat fissure burr may be used but may lead to more microtrauma and difficulties in reestablishing normal occlusal pattern and correcting more minor lesions and are therefore not recommended for dentistry. This procedure may need to be repeated at one- to 6-month intervals. The animals should be gradually switched over to a more natural diet that includes more grass hay and less pelleted feed in the intervening time. In chronically affected animals, revisits at 6- to 8-week intervals may be required for cheek tooth reductions for the rest of the animal's life.

Cheek tooth extraction may be necessary in cases of tooth root abscesses. It is important to protect the empty sockets to prevent impaction of food debris with subsequent abscessation. Commercially available gel preparations are available for this purpose. Incisors are usually readily removed using a dedicated rabbit luxator. Cheek teeth can be removed intraorally using a dedicated rabbit cheek teeth luxator and grasping forceps. Intraoral cheek teeth extraction may be very difficult to perform in guinea pigs and chinchillas. In some cases, an extraoral approach through a mandibular osteotomy may be indicated (see Chapter 3). The opposing tooth may or may not continue to grow and may need regular trimming.

Prevention

Animals with malocclusion should not be used for breeding. Because of the long narrow mouth and fleshy tongue of these species, adequate examination of the teeth is difficult, even with cheek dilators in a heavily sedated animal. Radiographs should be considered a necessary and routine diagnostic procedure whenever dental problems are suspected, to ensure adequate inspection of all bony structures. CT is often particularly useful for the evaluation of dental disease in small mammals, including diagnosis and treatment planning, and can provide more information than standard radiographs. Endoscopic guided dental examination is also recommended for a more thorough evaluation and screening.

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MASTITIS

Hosts

Guinea pigs, rabbits, rats, and hamsters are affected most commonly.

Etiology

Acute inflammation of the mammary gland is most often encountered during lactation, when milk provides an excellent medium for bacterial growth, the glands are pendulous and easily injured, and the young traumatize the teats. Mastitis is established when one or several genera of microorganisms (*Pasteurella* spp., *Klebsiella* spp., coliform bacilli, *Streptococcus* spp., *Staphylococcus* spp., or *Pseudomonas* spp.) enter the gland via the bloodstream, through a cutaneous lesion, or via the teat canal.

Predisposing Factors and Clinical Signs

An unsanitary environment, abrasive bedding, inappropriate caging, biting young, and mammary impaction after early weaning or death of neonates predisposes the dam to mastitis. The affected glands become diffusely or focally enlarged, firm, hyperemic, warm, and cyanotic. One or more glands may be affected and glands may dribble purulent material. Depression and death from septicemia or toxemia often follow.

Among companion and laboratory rabbits and rodents, guinea pigs are most often affected with mastitis. Causative agents are usually an alpha-hemolytic *Streptococcus* spp. or *E. coli*, although *Klebsiella* spp. and *Staphylococcus* spp. may also be involved. In acute cases, the affected gland is red-purple, and the milk may appear bloody. Maternal neglect of sucklings and death of the sow usually occur within hours to days. A chronic, suppurative mastitis may occur also.

Rabbit mastitis may be diffuse or focal and suppurative. When it is diffuse, the lesion is known as "blue breasts" or "caked udder." Affected rabbits are usually lactating and *Staphylococcus* spp., *Pasteurella* spp., or *Streptococcus* spp. are generally the causative agents. Clinical signs include fever that exceeds 40 °C (104 °F), anorexia, depression, death of neonates, and death of the doe from septicemia.

In rats, small isolated mammary gland abscesses are more common than acute diffuse mastitis. *Rodentibacter* spp. and *S. aureus* are often cultured.

A case of mastitis was reported in an 11-month-old hamster due to a galactogenic *E. coli* infection. Incisors from suckling pups were believed to be the source of trauma. Clinical signs included firm discrete subcutaneous nodules.

Treatment and Prevention

Treatment of an acute infection in rabbits includes lancing and flushing or debriding the abscesses, if present, and administration of antibiotics. All glands should be examined carefully for signs of infection. Trimethoprim–sulfa or enrofloxacin may be useful antibiotics for treating mastitis in small rodents. The infected animal's environment should be disinfected.

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MOUSEPOX (ECTROMELIA VIRUS)

Hosts

The mouse is the only natural host of ectromelia virus, which causes mousepox in many countries worldwide. The term ectromelia refers to an absence of or shortening of a limb. Experimental infection of other laboratory rodent species with this virus results in a brief, noncontagious infection with antibody production. Epizootic mousepox has occurred in many areas of the world for decades. This highly infectious and potentially devastating disease occurs as sporadic outbreaks in North America, generally associated with using contaminated

biologics in susceptible mouse strains. Clinically, the disease is most severe among certain inbred strains, especially BALB/c, DBA, CBA, C3H, and A. C57BL/6 strains are resistant, and infections are frequently inapparent.

Etiology

Ectromelia virus is a large (175 × 290 nm), oval-to-brick-shaped, cytoplasmic, double-stranded DNA orthopoxvirus, with a characteristic dumbbell-shaped nucleus. It is classified in the family Poxviridae, Vaccinia subgroup, and is similar to vaccinia and variola in many ways.

Transmission

The virus is stable in dry environments. The probable transmission routes are respiratory aerosol, biting and skin abrasions, contact with skin debris, excretions from the oropharynx and genital tracts, cannibalism, and ingestion of contaminated feces. The virus is excreted from the intestinal tract for long periods after infection.

Urine, ectoparasites, other animals, humans, fomites, and infected tissues or biologics may disseminate the virus. Approximately 10 days after infection, characteristic skin lesions develop, and virus is shed into the environment. The virus is spread from cage to cage by animal handlers and among institutions by investigators who exchange infected mice or mouse tissues, for example, tumors, cell lines, hybridoma lines, and sera. The virus in these products may remain viable in ultracold freezers for decades.

Predisposing Factors

Different mouse strains vary in susceptibility to ectromelia virus, although such differences have been determined on the basis of a few outbreaks. In recent outbreaks high mortality was observed among BALB/c, DBA, A, and CBA mice. Mice of these strains tended to die suddenly with few or no skin lesions. C3H mice were susceptible, but death was delayed, and skin lesions developed frequently. C57BL/6 and black congenic strains of mice were resistant.

Clinical Signs

Mousepox infections may be asymptomatic, latent, acute, subacute, or chronic. Clinical signs vary widely, and the nature of clinical disease expressed is dependent largely on mouse genotype. The acute, systemic form of infectious mousepox with high morbidity and mortality occurs in epizootic outbreaks in susceptible strains. Clinical signs of acute mousepox include hunched posture, rough hair coat, conjunctivitis, swelling of the face or extremities, diarrhea, and high mortality. The cutaneous rash, an important source of virus dissemination, is seen seldomly in acute outbreaks.

The subacute-to-chronic, enzootic, or cutaneous forms involve a generalized papular rash with eventual swelling, ulceration, and amputation of appendages and variable mortality. The cutaneous lesions of mousepox may resemble those associated with mite allergies, *Corynebacterium* spp. arthritis infections, and bite wounds.

Necropsy Signs

The gross lesions associated with acute mousepox are hyperemia and edema of the viscera, enlarged Peyer's patches, lymphoid hyperplasia, splenomegaly, a peritoneal exudate, and, as the disease progresses, hemorrhage into the intestinal lumen and focal necrosis of the spleen, liver, pancreas, lymph nodes, thymus, and other organs.

In the subacute-to-chronic forms, focal necrosis becomes more extensive; the vesicular, cutaneous pox lesions become crusted; and swelling and necrosis of the extremities occur. Scars in the spleen are pathognomonic for prior ectromelia virus infection.

Histopathologic changes are characterized by massive splenic necrosis that originates in the lymphoid follicles and spreads throughout the organ. Hepatic necrosis often involves a large portion of the liver. Necrosis of Peyer's patches, lymph nodes, and thymus resembles microscopic changes seen in the spleen. Characteristic eosinophilic, type A, cytoplasmic inclusions can be found in infected epithelial cells early in the rash at sites of focal epidermal hyperplasia and erosion. Infected hepatocytes adjacent to areas of hepatic necrosis contain basophilic, type B, intracytoplasmic inclusion bodies.

Diagnosis

Mousepox is diagnosed by clinical and gross necropsy signs and by the demonstration of intracytoplasmic, eosinophilic inclusion bodies (Marchal bodies) in the epithelial cells of the skin, small intestine, and pancreas. When inapparent infections are suspected, susceptible, disease-free mice can be introduced into the colony as sentinel animals.

Finding splenic and hepatic necrosis and other typical lesions allows a diagnosis of acute mousepox. Confirmation is achieved through electron microscopy of affected organs, which reveals characteristic poxviruses. Caution is necessary because vaccination with live vaccinia virus may introduce viruses with the same morphologic characteristics as the natural infection. The virus can be isolated from the spleen and liver during early stages of disease by culture on mouse fibroblasts (L929), Vero, or HeLa cells, and it grows well on the chorioallantoic membrane of hen's eggs. Virus can be demonstrated in tissues by immunocytochemical methods, for example, fluorescent antibody.

Serologic testing is useful for screening suspect colonies and for detecting latent infections. Possible prior vaccination is a consideration in interpretation of serologic results. The IHD-T strain of vaccinia virus is used commonly in vaccination outside of North America; however, no hemagglutination-inhibiting antibody is produced, and the HAI test can be used

for screening vaccinated colonies. Vaccination interferes with the more sensitive ELISA and IFA tests. The ELISA test or PCR is more sensitive and is used commonly as the primary serologic test. The IFA test is highly sensitive and specific and is used as a secondary or confirmatory procedure.

Treatment

A satisfactory treatment does not exist for infectious mousepox. Vaccination using a live IHD-T strain of vaccinia virus cultured in egg embryos may be used to limit outbreaks in small, closed colonies; however, elimination of affected colonies is preferred to preclude the possibility of establishing an enzootic disease.

Prevention

Selection of ectromelia-free stock, careful husbandry and quarantine measures, serologic screening tests, and the use of disease-free, susceptible, sentinel mice are measures used to prevent latent carriers from entering the colony. Particular care should be taken with inbred and congenic strains from sources where mousepox has been enzootic. Imported mice or mouse tissues, mice from unknown sources, or suspect mice should be strictly quarantined. Mouse tissue destined for transmission to susceptible mice should be checked for ectromelia virus by passage through susceptible hosts or tested via MAP or PCR assays. Infected colonies must be eliminated, and rooms and equipment sanitized and disinfected thoroughly because the virus remains viable in dry environments. Several disinfectants are effective: vapor phase formaldehyde, iodophores (150–300 ppm), and sodium hypochlorite (1,000 ppm available chlorine). Dead animals, animal wastes, and contaminated bedding should be isolated and incinerated. Movement into and out of suspect colonies should be strictly limited. Intrauterine infections with ectromelia virus limit the effectiveness of hysterectomy derivation to eliminate the infection.

Public Health Significance

Humans are not susceptible to infection by the ectromelia virus.

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MURINE ENCEPHALOMYELITIS

Hosts

Laboratory mice and rats are the natural hosts of generally asymptomatic infections with Theiloviruses, the causative agent of murine encephalomyelitis viruses (MEV; previously TMEV). The disease is sometimes referred to as mouse polio. Wild mice may be a source of infection. Laboratory rats, Syrian hamsters, and infant cotton rats can be infected experimentally with the mouse strains. Rats also have their own distinct strains of theilovirus (RTV) and commonly demonstrate weak cross-reactive titers to the mouse GDVII theilovirus strain in routine ELISA serodiagnostic testing. No lesions have been reported in rats.

Etiology

Theiloviruses are picornaviruses (RNA) and strains vary in their virulence for mice. GDVII and FA, both highly neurovirulent strains, and Theiler's original (TO) are among the more widely studied and reported strains. There may be differential rodent strain susceptibility to viral infection in mice and rats, and sentinels or other colony animals should be selected carefully if this agent is to be detected. For example, one study suggested that Sprague-Dawley rats are more susceptible to RTV infection with longer periods of viral shedding than cesarean-derived (CD) rats, despite their common ancestry. Similar strain-related differences in susceptibility are noted in mice. BALB/c and C57BL/6 mice tend to be resistant, whereas DBA/2, SJL, SWR, and CD-1 outbred mice are more susceptible.

Theiloviruses should not be confused with the encephalomyocarditis viruses, which are picornaviruses with a predilection to cause heart damage.

Transmission

Spread of the infection is exclusively by the fecal–oral route because most strains of the virus that infect mice naturally replicate in the intestine. In colonies that are infected enzootically, mice become infected around the time of weaning, at approximately 3 weeks of age. In infected colonies, mice normally develop immunity, and only a small percentage (e.g., <1%) may develop clinical disease. In the typical disease, affected mice develop flaccid posterior paralysis with or without convulsions. Severity of CNS signs is viral strain, host age, and genotype dependent. Unlike the transient intestinal infection, the virus in the CNS form of the disease may persist in the brain and spinal cord for the life of the mouse.

Clinical Signs

Infections with wild-type rodent strains of Theilovirus are usually subclinical; however, small numbers of mice may develop an extended viremia with dissemination of the virus to the spinal cord and brain, causing paralysis of the rear legs (rarely), circling, rolling, and other signs of CNS disease. There is little or no mortality. Signs of CNS disease in mice are by no means pathognomonic of mouse polio, and CNS signs in mice may be associated with disease processes other than mouse polio.

Necropsy Signs

In mice with CNS signs, there is nonsuppurative meningoencephalitis and myelitis with selective involvement of the gray matter. In SCID mice, marked vacuolation of neurons and glial cells in the cerebrospinal axis is a feature of the disease.

Diagnosis

Clinical signs are of limited value due to their low prevalence. Diagnosis is based usually on serologic testing using either ELISA or IFA tests. Viral isolation, PCR testing, microscopic immune-related lesions of poliomyelitis, and demyelination in the CNS are useful also in establishing a diagnosis. Infection may resemble polio of humans.

Infected mice are an important model of polio and multiple sclerosis in humans; therefore, this disease of mice has been studied extensively. Much of the credit for the current success in controlling human polio worldwide can be attributed to research using laboratory mice in polio research.

Control and Prevention

Use of barrier conditions and mice proven free of mouse polio by serologic testing are the methods used most commonly to prevent introduction of the disease into viral-free mouse colonies. Hysterectomy and rederivation are effective means of eliminating the infection.

Public Health Significance

A number of theiloviruses have recently been isolated from human clinical cases, one of which was a child with severe respiratory disease. The relationship to rodent exposure is unknown.

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MURINE MYCOPLASMOSIS

Hosts

Rats and mice are the principal natural hosts of respiratory and genital infections caused by *M. pulmonis*. Infection and disease are common in companion animals, nonbarrier-housed rats and mice, and wild rodents. Rabbits, guinea pigs, and other rodents may on occasion carry the organism, but they are generally not affected clinically.

Etiology

Mycoplasmas are very small pleomorphic organisms with no distinctive cell wall. They are bounded by a triple-layered membrane. They vary from ovoid-to-filamentous forms. *M. pulmonis*, which may accompany viral or bacterial infections, is an extracellular pathogen that colonizes mucosal surfaces and is responsible for the clinical signs and lesions of murine mycoplasmosis. Bacteria that may accompany *M. pulmonis* in respiratory disease include *Rodentibacter* complex, *Actinobacillus* spp., *Streptococcus pneumoniae, B. bronchiseptica*, *Filobacter*, and *C. kutscheri*.

Mycoplasma arthritidis, though usually causing inapparent infections of rats and mice, may cause polyarthritis in rats with swelling of joints and toes.

Transmission

M. pulmonis is carried in the upper respiratory tract. Transmission of contagious mycoplasmal infections is by direct contact between mother and young, respiratory aerosol over short distances, sexual transfer, exposure to animal carriers, and in utero passage.

Predisposing Factors

Agents that damage the protective capacity of the respiratory epithelium predispose to *M. pulmonis* infection. Such agents include ammonia, sulfur dioxide, Sendai virus, and various

bacterial infections. Ammonia gas in an animal colony is generated from urine and feces by urease-positive bacteria. Factors that are involved in ammonia accumulation include poor ventilation and sanitation, cage crowding, bacterial growth, and room overheating. The metaplastic and ciliary-inhibiting effects of ammonia can extend an innocuous upper respiratory infection into a bronchopneumonia.

Clinical Signs

Although *M. pulmonis* infections are usually subclinical, at least to the casual observer, clinical signs occur and represent three major foci of infection: upper respiratory tract, lower respiratory tract, and urogenital tract. In all areas, the clinical onset is usually slow and progressive, but acute episodes may occur in young and susceptible animals.

The upper respiratory disease, involving the nasal passages and middle ears, is signaled by sniffling, occasional squinting, rough hair coat, and sneezing. If the inner ear becomes involved, torticollis or head tilt may occur.

Lower respiratory disease is initiated or exacerbated by ammonia gas, bacterial infections, or Sendai virus infection, and is characterized by lethargy, rough hair coat, hunched posture, chattering, weight loss, labored breathing, and eventually death. Porphyrin may accumulate around the eyes and external nares. Unless the respiratory infections are complicated by a bacterial infection, the terminal clinical stages of mycoplasmosis may last weeks or months. Geriatric pet rats commonly develop this form of the disease.

In the ascending genital infection, which is common, infertility, embryonic resorptions, and small litters are seen.

Necropsy Signs

Upper respiratory infection is characterized by serous-to-purulent inflammation in affected tissues. In murine mycoplasmosis, unilateral or bilateral otitis media is a common finding, often the only gross abnormality. The pulmonary lesions in the early stages of the disease are well-demarcated foci of firm red or gray atelectasis and consolidation. As the disease progresses, inflammatory debris accumulates in the air passages, resulting in bulging, muco-purulent areas of bronchiectasis that give the lung a "cobblestone" appearance. The content of these lumps is pyogranulomatous and yellow-gray (Figure 5.19).

Microscopic lesions may be acute or chronic and begin with neutrophils in airways, hyperplasia of mucosal epithelium, and lymphoid proliferation in the submucosa of the bronchi and progress to bronchiolar invasion, consolidation, bronchiectasis, and pulmonary abscesses.

The genital infection, which may exist independently of the respiratory infection, is an ascending process that may involve the entire reproductive tract. Older females are more often affected. Metritis, pyometra, and purulent oophoritis and salpingitis characterize the serious genital infection.

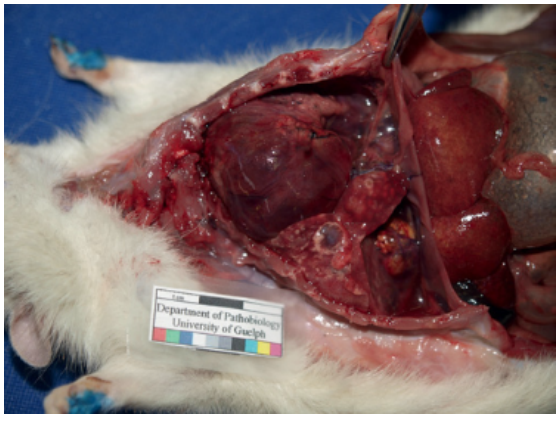


FIGURE 5.19. Chronic *Mycoplasma pulmonis* infection in a rat at necropsy. The affected lung has multifocal areas of pyogranulomatous inflammation, atelectasis, and consolidation contributing to a "cobblestone" appearance.

Diagnosis

Diagnosis of murine mycoplasmosis is based on clinical signs and can be made presumptively based upon serologic tests (ELISA, MFIA, or IFA; see Chapter 3 for a fuller description of these terms). Definitive diagnosis is based upon gross and microscopic lesions and on the cultural isolation of *M. pulmonis* from the nasal pharynx, tympanic bullae, trachea, uterus, or lungs. The organism may be carried in the upper respiratory passages in the absence of clinical disease. Culture of *M. pulmonis* requires special media enriched with yeast extract and 10% swine or horse serum. The plates are incubated at 37 °C in an atmosphere of normal or reduced oxygen and increased humidity. PCR assays are also available and can be used on lavage fluid. For colony health monitoring, sentinel animals need to be in direct contact with infected animals for transmission to occur.

Filobacter infections may produce lesions that resemble those associated with respiratory mycoplasmosis. A distinguishing feature is that large numbers of *Filobacter* can be found among cilia in the ciliated respiratory epithelium of the nasal passages, trachea, and other airways in silver-stained sections. An ELISA test can be used to detect serum antibody to *Filobacter*.

Treatment

Elimination of mycoplasmal infections in large populations of rats and mice is, for all practical purposes, impossible without rederivation. Antimicrobials placed in the drinking water may have a palliative effect, suppressing clinical signs. Tetracycline hydrochloride at 5 mg/mL given fresh daily for five days or longer in deionized drinking water may suppress clinical signs if rats drink the concentrated solution. Others have suggested that adding tetracycline to the drinking water is ineffective in controlling infectious disease and may, in fact, be detrimental

in other ways. Some tetracycline solutions at this concentration in tap water form a scale that blocks the sipper tube. Use of distilled water reduces this effect. Lower levels of tetracycline may help to reduce secondary bacterial complications. *In vitro*, tetracycline and tylosin have been more effective against *M. pulmonis* than are tiamulin, spectinomycin, lincomycin, and gentamicin. Enrofloxacin at 5–10 mg/kg every 12 hr IM, SC, or PO combined with doxycycline hyclate, 5 mg/kg PO every 12 hours, for 5–10 days may suppress clinical signs. Antimicrobial agents given by nebulization in combination with bronchodilators may also help.

Sulfamethazine at 0.02% in the drinking water or 1 mg/4 g feed or tylosin at 66 mg/L (2.5 g/10 gal) for 21 days are other treatment suggestions, but the prognosis for recovery remains poor, and treatment should not be advocated as a method to eliminate *Mycoplasma* spp. from a colony.

Prevention

Prevention of murine mycoplasmosis involves placing rodents free of *M. pulmonis* into a barrier facility. Strict husbandry standards, exclusion of wild rodents, serologic and postmortem monitoring, good ventilation, and low population densities in the cage and room help to maintain a colony free of *M. pulmonis*.

Public Health Significance

M. pulmonis has been detected, isolated, and sequenced in animal facility workers exposed to infected rats. The mode of transmission is unknown but likely requires direct contact or aerosolization.

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MURINE NOROVIRUS INFECTIONS

Host

To date, the only known host for this virus is the mouse.

Etiology

Mouse norovirus is a single-stranded RNA virus within the Caliciviridae family. The virus was first reported in mice in 2003, from a colony of immunodeficient mice (RAG/STAT−/−) experiencing increased mortality. Subsequently, the virus was isolated and characterized as a norovirus, named murine norovirus 1 (MNV-1), and it was thought that a requirement of STAT1-dependent innate immunity had to be present for resistance to the murine norovirus. Mice lacking both interferon α/β and interferon γ receptors are also very susceptible to lethal infection, demonstrating that interferons are needed for resistance to MNV-1. At least six distinct strains have been identified to date. In any regions where viral monitoring has been initiated in recent years, the prevalence of MNV has been high and reported at 30% or greater.

Transmission

The virus is thought to be transmitted by the fecal–oral route. Although autoclaving of materials is also effective, a 1 : 10 dilution of bleach is the only disinfectant that is currently known to kill the virus. Quaternary ammonium compounds and mild detergents are ineffective. Rederivation is an effective means for exclusion of MNV-1 from susceptible populations. Cross-fostering pups from MNV-positive dams to MNV-negative dams within 3 days of birth is also highly effective at eliminating the virus from infected colonies. The infection is chronic.

Predisposing Conditions

Defects in innate immunity were initially thought to be necessary for viral infection. Mild histologic lesions have been noted in subclinically infected immunocompetent outbred

mouse stocks, suggesting that there may be a significant inter-strain variability in infection and disease susceptibility.

Clinical and Necropsy Signs

MNV inoculation of RAG/STAT−/− mice, which have defects in both innate and acquired immunity, leads to lesions of encephalitis, cerebral vasculitis, pneumonia, meningitis, and hepatitis. Immunocompetent mice (129 wild-type) seroconvert to MNV-1 capsid protein after oral or intracerebral inoculation but have no clinical signs or tissue pathology. These mice have only a transient infection as evidenced by a lack of viral RNA from tissues by three days postinoculation. In mice deficient in T and B lymphocytes, MNV-1 causes persistent infection but no clinical signs.

Histologic lesions (mild, multifocal hepatic necrosis) have been reported in outbred sentinel female mice (Swiss-Webster). In this naturally occurring outbreak, there were no clinical or gross signs in affected mice; however, animals were serologically positive and had histologic lesions consistent with the infection in the liver (cross-reacted with MNV antibodies by IHC).

Diagnosis

The virus can be detected by serology (MFIA, IFA, and ELISA), but this requires careful selection of sentinel animals. CD-1 mice showed poor-to-no seroconversion at 3 weeks postinfection. Animals maintained on dirty bedding also showed a poor antibody response at 4 weeks postexposure, but this was improved after 5–6 weeks of exposure. These findings point to the need for a longer period of time before detectable antibodies are present in the serum compared with other viruses. PCR can be used to detect MNV-2, -3 and -4 from the spleen, jejunum, and mesenteric lymph nodes at up to 8 weeks postinfection. Jejunum and mesenteric lymph nodes are the best tissues to select. In one study, fecal shedding was still reported for MNV-2, -3, and -4 at week 8 postinfection.

Public Health Significance

Currently there is no evidence for zoonotic transmission of MNV.

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MYIASIS (FLY STRIKE)—PRIMARY

Hosts

Cuterebriasis is a type of primary myiasis in which the insect requires a specific living host for the larvae to feed on. It occurs primarily in rabbits and rodents housed outdoors or allowed access to the outdoors. Incidental hosts include humans and other animals. At least 10–70% of wild cottontail rabbits (*Sylvilagus* spp.) are infected depending on geographic location and season.

Etiology

In North America, cuterebriasis is caused by larvae of bot flies, *Cuterebra* spp., and is found commonly in lagomorphs and rodents. The three larval stages are pathogenic, whereas the adult, whose short life span is dedicated mainly to breeding, is seen rarely. After hatching, bot fly larvae become buried subcutaneously, each with a breathing pore, after migrating randomly from their point of entry. Not only do the larvae cause lesions in different organs and tissues, but they also create conditions favorable for secondary bacterial infections and adverse immunologic reactions. In cases wherein larvae wander aberrantly to a sensitive tissue such as the brain, they may cause the death of an animal.

Predisposing Factors

Rabbits that are housed outdoors or allowed to roam freely in yards and fields are more likely to be exposed to bot flies and larvae. Because juvenile mammals tend to be more exploratory in nature and because their immunity is not yet developed fully, they are more likely to acquire cuterebriasis with adverse reactions. Marginal husbandry and management practices, such as neglecting wet, dirty, and diseased animals with gaping wounds or open sores, predispose the animal to attract flies, especially in the summer months.

Transmission

Cuterebra spp. are obligate myiasis flies that deposit their ova in nests, logs, and burrows frequented by wild lagomorphs and rodents. The ova hatch into first-stage larvae and wait for susceptible animals to pass by. The larvae then cling to the passing host or are mechanically passed to other contact hosts. The life cycle is complex and occurs primarily in the definitive host.

Clinical Signs

Depending on the number, location, and developmental stages of the parasites, as well as the health and age of the host, the clinical signs of cuterebriasis may vary from inapparent infection to severe toxic shock. The relatively large larvae are generally found in subcutaneous sites on the back or rump area, front shoulder, neck or throat area, and ventral abdomen. Juvenile animals with greater than 9–10 bot flies may succumb with toxic signs. Clinical laboratory tests of infected hosts revealed anemia, alterations of CBC, WBC, and plasma proteins, as well as reduced fertility. Aberrantly migrating larvae have been reported intranasally, intraocularly, intraorally, and intracranially, where they may cause severe CNS signs that should be differentiated from the clinical signs of rabies. Crushing the *Cuterebra* spp. larva in the subcutis may result in a fatal shock reaction. Additionally, death may ensue due to progressive debility resulting from chronic infection. If the animal survives, it loses considerable body condition and becomes a prime candidate for secondary bacterial infections and other complications, including predation.

Necropsy Signs

Gross lesions of *Cuterebra* spp. are found mainly in the subcutis where they are associated with dead or live larvae and their breathing pores. In cases of aberrant migration, larvae may be found almost anywhere, especially in the brain, middle ear, or nasal passages. Because death may occur as a result of the toxins produced by the larvae, gross lesions in other areas of the body may be absent. Animals that die from chronic infection may be grossly emaciated with apparent splenomegaly, lymph-node enlargement, and cachexia.

Histologically, the severity of the infection is difficult to assess; however, marked inflammatory reactions and fibroblast proliferation are usually associated with aberrant migration of the larvae in certain organs.

Diagnosis

Diagnosis of cuterebriasis depends on finding boil-like or furuncular lesions associated with a fly larva. Furthermore, the larva is located by a 1–3 cm cone-shaped swelling with an apical pore. Careful dissection of the pore may reveal a *Cuterebra* spp. larva in the first, second, or third stage of development. The larva is club-shaped with tapered ends and has a segmented body with circumferential rows of caudally projecting, spine-like denticles used for orientation. The mouth contains a pair of hooks, whereas the tail end contains the stigmatic plates used for breathing through the subcutaneous pore.

Treatment

Treatment may involve shaving the hair and surgical preparation of the affected skin. The *Cuterebra* spp. larva is killed with alcohol, the pore is opened surgically, and the larva is removed carefully and intact. The resulting wound is kept dry and clean to facilitate rapid healing. Ivermectin has been used experimentally in cases of aberrant migration, but reaction to the dead larva is potentially fatal, necessitating concurrent use of corticosteroids.

Prevention

Prevention of myiasis in rabbits is accomplished with effective fly control measures such as proper disposal of manure, screened windows, fly traps, and use of safe insecticides and fly repellents. In addition, pet rabbits may be groomed prophylactically to remove fly ova, and access to the outdoors should be restricted during fly season. Dead and infected rabbits should be disposed of immediately and properly to prevent *Cuterebra* spp. larvae from migrating to other rabbits.

Public Health Significance

Rabbit bot flies occasionally infect humans, especially children and the elderly. Cases of humans with intranasal, intracranial, and intraocular larval migration have been reported.

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MYIASIS (FLY STRIKE)—SECONDARY

Hosts

Secondary myiasis occurs when flies that normally feed on decomposing organic matter or carrion develop in wounded, soiled, or immobilized animals. Flies causing secondary myiasis are opportunistic and will lay eggs indiscriminately. Fly strike occurs primarily in injured or debilitated rabbits or rodents housed outdoors but may also occur in indoor pets.

Etiology

Secondary myiasis is caused by Calliphorid flies, also called blow flies, which have characteristic metallic blue or green bodies. Common names also include "bluebottle" and "greenbottle" flies. These flies feed and lay ova on urine- or feces-stained fur and decaying flesh in exposed, untreated wounds or sores. The ova hatch and larvae, which are called maggots, are found locally and superficially. Marginal husbandry and management practices, such as neglecting wet, dirty, and diseased animals with gaping wounds, open sores, or soiled perineal areas, predispose the animal to attract flies, especially in the summer months when these animals are housed outdoors.

Predisposing Factors

Animals housed outdoors with blood, purulent or necrotic debris, feces, or urine on their fur will attract flies. Diseased and moribund animals that are non-ambulatory with decubital ulcers become an easy target for flies to lay ova that hatch and become maggots. Accumulation of urine and fecal material around the perineum occurs in long-haired or obese rabbits, or those with hind end paralysis following spinal trauma. Animals that are neglected or handled rarely are more likely to develop conditions favorable to fly strike.

Transmission

Blow flies are opportunistic and will lay large numbers of eggs in any suitable location. Adult female blow flies deposit approximately 250 eggs at a time, which hatch into first-stage maggots within 24 hours. They feed and then molt into second-stage maggots, which feed for approximately 24 hours, and then molt into third-stage maggots. After more feeding, the third-stage maggots move away from the body and metamorphose into adult flies.

Clinical Signs

Clinical signs of fly strike are varied depending on the precipitating condition. General signs include depression, hunched appearance, reluctance to move, and unkempt hair coat. Maggots are not always readily visible, especially if they are covered by a mat of soiled hair, and owners are not always aware of the extent of the infestation.

Diagnosis

Maggots are usually associated with wounds, open sores, or wet folds of skin not readily accessible to the host when grooming. They are easy to see once hair mats and debris are cleared away. As in cuterebriasis, an overwhelming number of maggots on a rabbit or rodent may lead to terminal toxic shock.

Treatment

Animals should be stabilized with fluids, nutrition, and antibiotics if necessary, prior to maggot removal. Maggots and eggs should be removed, and the area washed with a generous amount of a mild disinfectant solution. The hair should be clipped around the affected area and an appropriate topical antibiotic applied several times daily until the wound heals completely. The animal should be confined indoors in clean, dry quarters during treatment. Any predisposing conditions, such as diarrhea, open wounds, or obesity, should be addressed to prevent recurrence.

Prevention

Prevention of myiasis in rabbits and rodents is accomplished with effective fly control measures such as regular disposal of uneaten greens and manure, screened windows, fly traps, and use of safe insecticides and fly repellents. Pet rabbits and rodents housed outdoors in the summer should be handled daily to detect any wounds, injuries, or diarrhea and may be groomed prophylactically to remove fly ova and soiled fur. Access to the outdoors should be restricted during fly season. Dead animals should be disposed of immediately to avoid attracting flies to the hutch.

Public Health Significance

Blow flies are opportunistic and may parasitize humans under the right circumstances.

MYXOMATOSIS

Hosts

Myxomatosis is a viral disease of wild (*Sylvilagus*) and domestic (*Oryctolagus*) rabbits. Wild rabbits are the natural reservoir host in North and South America. The virus causes localized firm skin tumors (fibromas) in wild lagomorphs.

Etiology

The disease is caused by several strains of myxoma poxviruses on the more virulent end of the myxoma–fibroma spectrum of viruses. The highly virulent variant that occurs in western California and Oregon is, appropriately named, the California strain. The virus is endemic in the *Sylvilagus* population in California. A variety of other strains exist in South America, Australia, and Europe. Substantial variations exist between strains of myxoma virus from different parts of North and South America, based on serologic and biologic comparisons.

Transmission

The highly virulent virus is transmitted mechanically from wild reservoir hosts primarily by arthropod vectors, mosquitoes, and flies. The extent of viral transmission varies with seasonal changes in populations of mosquitoes, mites, and fleas feeding on rabbits. Other arthropods can act as mechanical vectors, as might birds, plants, and fomites. In the United States, an annual increase in myxomatosis is seen from August to November.

Clinical Signs

The first clinical signs after infection with the California strain of virus include mild lethargy, red eyes, swollen eyelids, fever, and a watery ocular discharge. If the rabbit survives the acute stage, the reddening and swelling extend to the lips, face, ears, and anogenital areas. Death follows in a large percentage of unvaccinated rabbits. When rabbits survive, they develop cutaneous hemorrhages. Affected rabbits in the terminal stages of disease are anorectic and dehydrated. Some will survive and the lesions regress over 1–3 months. In subacute-to-chronic cases, the disease is often complicated by pasteurellosis, which causes additional deaths.

Unlike the more severe signs in *Oryctolagus cuniculus*, only localized tumors are produced by the virus in the reservoir host, *Sylvilagus bachmani*, in California. Lesions in animals with the European and South American disease forms include the development of skin tumors, which may eventually rupture and ooze.

Necropsy

Gross necropsy signs after infection of European rabbits with the California strain of virus are subcutaneous edema and widespread visceral hemorrhage. Microscopically, there is extensive epithelial proliferation with ballooning of cells in the stratum granulosum and hyperkeratinization in the overlying epithelium. Large, eosinophilic, intracytoplasmic inclusion bodies are seen in the stratum germinativum. Lymphocytic depletion occurs in the spleen, and necrosis of lymphatic tissue occurs in several organs. Mucinous skin tumors and capillary and venule endothelial proliferation develop in rabbits in Europe.

Diagnosis

Diagnosis is based on clinical signs, necropsy findings, and the characteristic histopathologic appearance of the lesions. Intracutaneous inoculation of suspect tissue into young susceptible rabbits will result in lesions at the inoculation site within a week.

Treatment

A treatment for myxomatosis does not exist. Results from a therapeutic trial with acyclovir were inconclusive. Effective commercial vaccines are available for use in companion and meat rabbits in some global regions, e.g., they are available in Europe but not in North America.

Prevention

Vector control through spraying, screening to exclude mosquitoes, avoidance of contact with wild rabbits, quarantine of new arrivals, and vaccination with live attenuated vaccines in the face of an outbreak are methods of preventing myxomatosis. Owners of companion rabbits in Australia are not permitted to vaccinate their pets against myxomatosis virus.

Public Health Significance

Myxomatosis virus does not affect humans.

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NASAL DERMATITIS (SORE NOSE) IN GERBILS

Hosts

Sore nose, rednose, or nasal or facial dermatitis occurs frequently in Mongolian gerbils (*Meriones unguiculatus*).

Etiology

Nasal dermatitis of gerbils is associated frequently with staphylococcal infections, but the primary cause may be the irritating nature of porphyrin-rich secretions from the Harderian glands that accumulate around the external nares, which are normally groomed onto the face and fur. *Staphylococcus* spp. are usually isolated from gerbils with nasal dermatitis, thus implicating this bacterium in the pathogenesis. In a breeding colony of Mongolian gerbils, *S. xylosus* was the predominant isolate obtained from sporadic cases of nasal dermatitis and was the primary *Staphylococcus* spp. cultured. The organism was considered an opportunistic pathogen.

Predisposing Factors

Gerbils are arid desert creatures and require an environment with low humidity for optimal skin health. In captivity, stressors such as changes in the cage, loss of or separation from cagemates, incompatible cagemates, and overcrowding result in increased chromodacryorrhea or red tears due to excess porphyrin-rich Harderian gland secretions. These secretions are removed normally by grooming with the forepaws over the pelage; however, accumulation of excessive amounts is irritating to the skin and may initiate sore nose.

Illness and depression or management conditions, for example, applying Elizabethan collars that reduce and prevent removal of porphyrin secretions by natural grooming behavior, may also predispose animals to this condition. Overcrowding stress in gerbils results in greatly increased activity, especially burrowing, or pressing the nose through cage wires, which aggravates facial irritation. Although the sore nose lesion may be initiated by the irritating effects of porphyrin secretions and aggravated by cutaneous abrasions incurred while burrowing, subsequent *S. aureus* or *S. xylosus* infection may perpetuate a chronic dermatitis.

Clinical Signs

Nasal or facial dermatitis in gerbils is seen as a red-brown hairless area on the snout surrounding and below the external nares. If spontaneous recovery does not occur, normal grooming behavior may cause the lesion to progress into a chronic moist dermatitis involving the face and the inner aspects of the forepaws. With severe signs, the gerbil may lose condition, become anorectic, and, uncommonly, may die. The prognosis is good with treatment.

Diagnosis

Clinical signs, predisposing factors, culture, and isolation of *S. xylosus* or *S. aureus* from the nasal lesions provide information to make a diagnosis.

Treatment

The condition may be alleviated by removing stressors, cleaning the face, using clay or corncob bedding products instead of wood shavings or chips, and by applying appropriate ophthalmic ointments. Antibiotic sensitivity testing may be useful to effect more precise therapeutic measures for treating chronic ulcerative nasal dermatitis. Both chloramphenicol palmitate and gentamicin have been used effectively to treat sore nose. Streptomycins should be avoided in gerbils because of toxicity.

Prevention

Chromodacryorrhea and nasal dermatitis may be controlled by adherence to good husbandry and management practices. Elimination of environmental and social stressors, such as overcrowding, fighting, and disease, is important. Provision of dust baths or absorbent, fine bedding material such as clay will help to ameliorate the disease by reducing the amount of porphyrin accumulation on the face. In one study, surgical adenectomy of the Harderian glands prevented the occurrence of sore nose by eliminating the source of porphyrin in collared animals.

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NEOPLASIA

General Discussion

Although literature surveys of the incidence of neoplasia in rabbits and rodents contain lengthy lists of tumor types, each species, if not each strain, possesses a limited number of common tumors. Therefore, although a limited number of tumors are described in this section, individual animals may develop one or more of a variety of neoplasms.

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Neoplasia in the Rabbit

Adenocarcinoma of the uterine endometrium is the most common spontaneously occurring tumor of rabbits. Its occurrence is influenced by genetic background, age, and endocrinologic factors. Tumors are rarely seen in commercial rabbitries and research institutions because of the young age of the rabbits in these populations.

Uterine adenocarcinoma has been reported more often in tan, French silver, Havana, and Dutch breeds and less often (in descending order) in the Marten, English, chinchilla, Beveren, sable, Himalayan, and Polish breeds. The tumor was not found in the Belgian and rex breeds. Rabbits of the higher-incidence breeds younger than 3 years have an incidence of approximately 4%, whereas rabbits older than 3 years have an incidence of uterine adenocarcinoma approaching 50–80%.

The association of uterine adenocarcinoma with pregnancy toxemia, pseudopregnancy, and hyperestrogenism remains controversial. The dose of estrogen and its carcinogenic effects may be important factors that influence the development of uterine cancer. Because rabbits are induced ovulators, a non-gravid doe is under estrogenic influences for most of the estrous cycle, which may play a factor in disease development. Further, a direct correlation exists between the incidence of uterine tumors and mammary carcinomas.

Senile atrophy of the endometrium may also predispose to tumor development. With increasing age, the endometrial cells, beginning deep in the glandular crypts, become less specialized, and the connective tissue stroma becomes less cellular and more collagenous. These progressive senile changes may underlie the transition to adenomatous, papillary, and cystic endometrial hyperplasia and then carcinoma. The hyperplastic stage lasts approximately 3 months, the carcinoma in situ 7 months, and the metastatic stage 10 or 12 months. The tumors are usually ovoid, firm, and hemorrhagic and are spaced regularly along the mesometrial junction. The neoplasm may invade the myometrium and seed the peritoneal cavity before hematogenous metastasis to the lungs and other organs occurs. Multiple uterine tumors may be of different sizes, but they are usually at the same stage of differentiation.

Clinical signs associated with uterine neoplasia in the rabbit include altered reproductive performance and eventually death over a period of 5–20 months after the tumor is first noted. During the subclinical period, affected does become less fertile, have smaller litters, abort or resorb fetuses, deliver stillborn kits, retain fetuses past term, and may have a bloody vulvar discharge or bloody urine. Typically, the multiple neoplastic nodules, which may be approximately 1 cm in diameter when first noticed, will grow to 5 cm by 6 months and can be palpated through the abdominal and uterine walls. The incidence or proportion of uterine tumors may decrease in SPF rabbits.

Lymphosarcoma is the most common tumor of juvenile and young adult domestic rabbits and is the second most common tumor of rabbits. Lymphosarcomas are characterized by pale, nodular enlargements in the renal cortices, hepatomegaly, splenomegaly, and intestinal lymphadenopathy. Cutaneous forms (epitheliotropic lymphoma) also occur.

A homozygous autosomal recessive gene may be necessary for development of lymphosarcoma. Lymphomas may be of either T or B cell origin.

Embryonal nephroma (Wilms' tumor) and bile duct adenomas rank third and fourth in tumor frequency in rabbits. It is tempting to speculate that bile duct tumors are a sequela of chronic *E. stiedae* infection. Squamous cell carcinoma is the second most common skin tumor after epitheliotropic lymphoma. Less frequently reported spontaneous neoplasms of the rabbit include testicular seminoma, thymoma, basal cell tumor, papilloma, squamous cell carcinoma, and osteogenic sarcoma with subcutaneous involvement.

The myxofibroma group of poxvirus-induced tumors occur as fibromas in *Sylvilagus* (cottontail) rabbits in both the eastern and western United States and in Europe, South America, and Australia. These antigenically related viruses are transmitted mechanically by mosquitoes and biting insects from cottontails to domestic rabbits, in which disease processes range from peracute, fatal myxomatosis to transitory single fibromas.

Myxomatosis, described elsewhere in this chapter, induces a generalized proliferation of reticuloendothelial cells and their mucin, which, with some strains of virus, results in the formation of irregular, subcutaneous, gelatinous tumors. These tumors, however, are not characteristic of the California disease.

A related poxvirus, endemic in Eastern cottontails (*S. floridanus*), causes self-limiting, subcutaneous fibromas in adult, domestic rabbits. In young *Oryctolagus*, the disease may become a disseminated fibromatosis. Prevention of the myxofibromatous diseases involves the exclusion of biting insects from the rabbitry and vaccination during an epidemic.

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Neoplasia in the Guinea Pig

Rhabdomyomatosis, an accumulation of glycogen-bearing myocardial cells and not a neoplasm, is visible grossly as pale foci on the mural and valvular endocardial surfaces of the atria and ventricles. Another nonneoplastic proliferation in the guinea pig is the embryonic placentoma, a multilayered transitory growth of parthenogenic origin that occurs within the ovary of the young female. The placentoma is resolved by fibrosis and may be related to the neoplastic ovarian teratoma.

True neoplastic processes are rare in guinea pigs, but an age-related increase in incidence has been noted. Estimates of the incidence of neoplasia in guinea pigs over 3 years of age range up to 30%. Pulmonary neoplasia, usually bronchogenic papillary adenoma, is the most common category of tumor in the guinea pig, comprising 35% of the total. Tumors of the reproductive tract, the mammary glands, and the hematopoietic system comprise the remainder of the more commonly seen guinea pig tumors. Mammary gland tumors may occur in both male and female guinea pigs, of which approximately 30% are locally invasive adenocarcinomas.

Skin tumors affect up to 15% of aged guinea pigs, particularly trichofolliculoma, a benign form of basal cell tumor that is readily removed under anesthesia.

Leiomyomas were the most common reproductive tract tumors in a colony of aged (average 48 months) female guinea pigs and were seen frequently in conjunction with cystic rete ovarii. There is likely a relationship between the estrogen-secreting cysts and development of leiomyomas (similar to estrogen-dependent growth of fibroids in premenopausal women).

Spontaneous lymphocytic leukemia is a commonly reported acute, virally induced (c-type RNA virus) malignancy with a rapid course. It is often fatal within 2–5 weeks of onset. Strain 2 inbred guinea pigs are uniquely susceptible. The hair coat of the affected animal becomes rough, the mucus membranes are pale (anemia), and the liver and lymph nodes are enlarged. The white blood cell count may reach 250,000/mm^3, and typical 18–40 µm leukemia cells are seen on blood smears. The disease responds favorably to chemotherapy.

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Neoplasia in the Chinchilla

There is a paucity of information available regarding tumors of chinchillas. In the past, the majority of chinchillas were raised for fur production and did not survive long enough to develop tumors. Despite the fact that chinchillas live to be 20 years old or more, tumors are rarely seen in practice. Uterine leiomyosarcoma, lymphoma, osteosarcomas, and pulmonary tumors have been reported.

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Neoplasia in the Hamster

The incidence of spontaneous neoplasia in the Syrian golden hamster is reportedly low. Variations depend on the source of the survey and the ages of the animals described. Reports vary from 4% as an overall population incidence up to 50% or more in select groups of hamsters over 2 years of age. Though the incidence of tumors is low, the variety of tumors in aged hamsters is large. Endocrine tumors of the adrenal cortex comprise the largest reported group. Next are tumors of the lymphoreticular system (predominantly lymphomas), tumors of the skin and subcutis, and tumors of the gastrointestinal tract (polyps, papillomas, and adenocarcinomas). Incidence

varies substantially from colony to colony. Most tumors are benign. Benign follicular thyroid tumors are seen occasionally, especially if there is an iodine deficiency.

One of the most frequent sites for spontaneous neoplasms is the hematopoietic system. Reported tumors include malignant lymphomas with peripheral lymph-node enlargement and lymphosarcomas. This is related to a hamster polyoma virus infection. Cutaneous lymphomas, resembling mycosis fungoides of humans, have also been reported in aging pet Syrian hamsters. Clinical signs included friable skin, hair loss, foul odor, erythroderma, dermal plaques with surface ulceration and crusting, papules, and lymphadenopathy, in addition to lethargy, anorexia, emaciation, and neuromuscular involvement. Progression of the disease was rapid, and systemic involvement was apparent at necropsy. A cutaneous hemangiosarcoma was reported in a 2-year-old female hamster with an ulcerated mass on its flank. The mass was removed surgically and did not recur.

Reproductive system tumors are infrequent and include thecomas and granulosa cell tumors of the ovaries, leiomyomas, and endometrial polyps of the uterus. Male reproductive tumors are rare, as are tumors of the central nervous system.

Tumors of the gastrointestinal system vary considerably between studies. In one report, polyps of the cecum and colon and gastric squamous papillomas were found. Cholangiomas (bile duct tumors) are common in some colonies, while cirrhosis is reported in others. Urinary system tumors are uncommon in hamsters. A wide variety of skin tumors have been seen. They include melanomas as the most common, followed by basal cell tumors, keratoacanthomas, squamous papillomas, Harderian gland adenomas, and warts. Hemangioendotheliomas of the vascular system are reported occasionally.

Hamsters are also susceptible to a range of experimentally induced tumors. The hamster's evertible cheek pouch is an easily accessed, immunologically protected site that was historically used for tumor transplantation. Immunodeficient mice have supplanted the use of the hamster cheek pouch for this purpose.

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Neoplasia in the Gerbil

The incidence of spontaneous neoplasia in gerbils older than 2 years is high. Neoplasms in gerbils cover a range of types, with tumors of the female reproductive system perhaps being the most common. Granulosa, thecal and lutein cell tumors, dysgerminomas, and teratomas have been reported in the ovary. Adenocarcinoma of the oviduct, uterine adenocarcinoma, and leiomyoma have also been reported. A few tumors of the male genital system have been reported: seminoma, teratoma, and prostatic adenomas. Adrenocortical adenomas and adenocarcinomas are also common tumors of gerbils. Neoplasms of the skin, which include those of the ventral scent gland, include basal cell carcinomas, melanomas, sebaceous adenomas, fibrosarcomas, squamous cell carcinomas, and cholesteatomas. Neoplasms have been reported in several other tissues. These include pancreatic islet cell adenomas, hepatic lymphangiomas, cecal adenocarcinomas, thymomas, splenic hemangiomas, Hodgkin's-like lymphoma, urinary hemangiomas, and osteosarcomas. Pseudoadenomatous structures of the skin, cystic ovaries, and periovarian cysts, which can cause infertility, are common, nonneoplastic processes that occur in the gerbil.

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Neoplasia in the Mouse

Neoplasia in mice is one of the most extensively investigated disease processes of rodents. Volumes have been written about the causation, pathogenesis, structure, and resolution of murine tumors. With the development of inbred strains and selection for tumor susceptibility and resistance, the pattern of tumor incidence in the laboratory mouse has become different from the pattern in its ancestor, the wild house mouse, or in the outbred white mouse. Neoplasia may be manifested clinically as weight gain or loss; cutaneous, subcutaneous, or abdominal swellings; infertility; paleness due to anemia from external or internal bleeding; increased susceptibility to infection; and death.

Adult, wild or random-bred, female breeder mice have the following approximate tumor incidences: pulmonary tumors, 28%; hemangioendotheliomas, 8%; ovarian tumors, 6%; mammary tumors, 6%; hepatomas, 4%; leukemias, 2%;

reticulum cell sarcomas, 2%; and subcutaneous sarcomas, 2%. Fibrosarcomas are also common in pet mice. A thorough discussion of representative inbred strains and their approximate tumor incidences may be found in *The Mouse in Biomedical Research,* 2nd ed., vol 2: *Diseases,* 2007.

Mammary tumors and lymphosarcomas are among the most common tumors of inbred strains. Some representative inbred strains and their associated neoplasms are mammary tumors in C3H mice, plasma cell tumors in BALB/c mice, type B reticulum cell sarcomas in SJL mice, and leukemias in AKR mice. More than 90% of AKR mice will develop leukemia by 1 year of age. Tumor incidence varies with sex, age, parity, diet, caloric intake, and substrain. Common experimental predisposing factors include radiation exposure and chemical carcinogens.

Mice develop a variety of spontaneous malignancies of the hematopoietic system, particularly of lymphopoietic origin. The incidence varies widely, depending on the strain of mouse, from 0 to virtually 100%. Similarly, environmental factors may also play a role in tumor development. Up to a 10-fold difference in the incidence of neoplasms may occur in the same strain maintained in different laboratories or under different environmental conditions. Thymic lymphoma is the most common malignancy of the hematopoietic system in the mouse. Histologically, the mediastinal mass is composed of lymphoblastic cells with numerous mitoses. Varying stages of differentiation may be observed. These tumors are of T cell origin. Committed T cells may originate in the bone marrow, then migrate to the thymus, where a thymic tumor develops. Thymic lymphomas are relatively common in SCID mice. Up to 20% of old *scid/scid* mice die with thymic lymphomas. Spontaneous thymic tumors are associated with endogenous retroviral infection and may be induced experimentally by chemical carcinogens (e.g., alkylnitrosamines).

Lymphopoietic tumors of B cell origin commonly affect spleen and lymph nodes with no thymic involvement. There may be infiltration of transformed lymphocytes into other tissues including liver, kidney, myocardium, leptomeninges, and so forth. Neoplastic cells often have large vesicular nuclei; prominent nucleoli, and abundant, poorly delineated cytoplasm, but tumors composed of relatively well-differentiated lymphocytes also occur. Cell type classification is similar to that used in other mammals.

Virtually all laboratory mice are contaminated with retroviruses. Unlike cells transformed by an oncogenic DNA virus, retrovirus-transformed cells may also produce infectious viral particles. Mice normally harbor endogenous retroviruses in a variety of types of cells, which are readily transmitted in germ cells to their progeny. Exogenous retroviruses also exist and are transmitted horizontally like conventional viruses but have largely been eliminated from laboratory mice. Retroviruses can also be transmitted horizontally via virus-containing urine, feces, milk, or saliva. There does not appear to be a good correlation between production of endogenous virus and spontaneous hematopoietic neoplasms. Frequently it appears that a chemical or physical carcinogen may be acting in concert with endogenous retrovirus to produce hematopoietic tumors. The two primary retroviruses that infect domesticated mice are murine leukemia virus (MuLV) and murine mammary tumor virus (MMTV).

Unlike the rat mammary tumor, which is removed easily, the mouse mammary adenocarcinoma is soft, fleshy, highly vascularized, and infiltrative. It cannot be removed without extensive tissue damage and hemorrhage.

Primary tumors of the lung are relatively common in the mouse, particularly in certain strains (e.g., BALB/c and C3H). These tumors do not appear to normally be virally induced but can be produced experimentally in mice by carcinogen administration. Thymectomized mice are more sensitive to induction of lung tumors than intact mice.

Although polyoma virus may infect cell lines and produce tumors in inoculated mice, hamsters, and guinea pigs, its occurrence as a natural infection is unlikely.

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Neoplasia in the Rat

As with the mouse and other rodents, the incidence of spontaneous neoplasia in the rat varies with the age, sex, strain, diet, caloric intake, endocrine factors, and environmental circumstances of the population surveyed. Incidence of neoplasia in rats is up to

87% in select rat populations older than 2 years of age. The most common tumor in the rat is the mammary fibroadenoma, followed by pituitary adenomas and testicular interstitial cell adenomas (Leydig cell tumors). Tumors reported less often include uterine endometrial polyps, malignant lymphomas, mononuclear cell leukemias, histiocytic sarcomas, fibrosarcomas, Zymbal's gland tumor, thyroid adenomas, and hemangiosarcomas. Polyoma virus infections do not occur naturally in rats. Fischer rat large granular leukemia is a major cause of death in aging inbred F344 rats. Clinical signs include weight loss, anemia, jaundice, and depression. The liver and spleen are markedly enlarged at necropsy. This strain is also highly susceptible to mesothelioma and interstitial cell tumors.

Mammary neoplasms are most often benign fibroadenomas and are common in female Sprague-Dawley rats. Adenocarcinomas comprise less than 10% of mammary tumors in the aged female rat. Benign mammary tumors, seen occasionally in males, are usually single and may grow to 8 or 10 cm in diameter. Mammary fibroadenomas are well demarcated, ovoid or discoid, firm, and nodular. Size, growth rate, color, and consistency vary. Larger mammary tumors of rats may become ulcerated, hemorrhagic, and necrotic. The tumor is well tolerated by the host until the mass hinders locomotion or a septicemia or toxemia results from the ulceration and necrosis. Rats with large tumors will eventually lose weight and die. The encapsulated tumors may be removed surgically, but they recur frequently in another mammary gland. Care should be taken to ligate the large vessels entering the mass. Because mammary tissue is distributed widely in the subcutis of murine rodents, mammary tumors may be found behind the shoulders, on the neck, on the ventral abdomen and flank, or around the tail base. Spaying female rats will reduce the incidence of tumor development. The tumors are prolactin-responsive and may develop in the presence of a pituitary adenoma.

Pituitary gland neoplasms occur frequently in older female rats, particularly those on diets high in protein or calories. Chromophobe adenomas, the most common type of pituitary tumors, are soft, non-secreting, and well circumscribed with irregular surfaces. Compression of brain tissue from chromophobe adenomas may cause hydrocephalus, head tilt, depression, and a variety of other clinical signs.

Lymphosarcoma and histiocytic sarcoma are seen with high frequency in aged animals. Lymphosarcomas tend to be multicentric, involving the mesenteric lymph nodes and spleen with terminal leukemia and neoplastic seeding of the hepatic parenchyma.

Other types of tumors occur spontaneously but are sporadic in nature.

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NEPHROSIS

Hosts

Chronic progressive renal disease is an important cause of morbidity and is common in most small mammal species. The incidence may approach 25% or more. The disease may be quite variable clinically and the most common presentations are described below.

Etiology

The specific etiologies of the chronic renal diseases in these species have not been determined fully and the causes likely differ by species. When evaluating azotemia in these species, it is important to determine whether the origin is prerenal, renal, or postrenal in nature, prior to planning a therapeutic course of action. Primary renal disease is seen more frequently in aged males and the severity is often strain-dependent. Inappropriate diet, ad libitum feeding practices with secondary obesity, excessive protein content, mineral imbalances, high-carbohydrate diets, and infectious processes such as bacterial pyelonephritis have all been suggested as factors in the pathogenesis of the disease. Microscopically, lesions suggestive of renal degeneration can be seen as early as 8 weeks of age in some strains of rats and mice. In many small mammals with renal disease, the clinical signs are inapparent until the renal disease is quite advanced. Polyuria and polydipsia are often present but may be difficult to detect in an individual if animals are group-housed or deeply bedded.

The earliest detectable serum chemistry change in rats with primary renal disease is hypoalbuminemia. Blood urea nitrogen and creatinine levels may remain near normal until kidney failure is imminent. Histologically, it is reported that tubular basophilia indicative of proliferation is seen prior to glomerular changes, suggesting that the condition in rats has both a degenerative and regenerative aspect. Both diet-induced and spontaneous nephrocalcinosis is also seen in rats and consists of calcium phosphate deposits within the interstitium and tubules. Hydronephrosis, pyelonephritis, neoplasia, and obstructive nephropathy due to the presence of calculi or protein plugs in the urethra of male rats have all been reported as potential underlying causes of renal failure in rats.

A large percentage of aging Syrian hamsters demonstrate amyloid deposition within the glomerular basement membranes,

in addition to other tissues. The condition is more severe in females. Hamsters may also develop polycystic disease, neoplasia, and a glomerulonephropathy similar to rats.

Urolithiasis is a common cause of renal disease in guinea pigs and chinchillas. Like rabbits, the calculi can be found anywhere within the renal system, including the renal pelvis. Clinical signs are dependent upon the location of the urolith, and animals may show lethargy, anorexia, hunched posture, and bruxism. Metastatic calcification, often iatrogenic in origin from feeding rabbit chow or inappropriate vitamin supplementation, is a common cause of renal failure in guinea pigs. Similarly, segmental nephro-sclerosis, amyloidosis, or pyelonephritis may underlie kidney problems in this species. Bacterial cystitis is more common in female guinea pigs, likely because of the shorter urethra.

Interstitial nephritis and glomerulonephropathies are common renal lesions in various strains of aging mice. Amyloid deposition may also be seen in the kidneys and may be either primary (familial) or secondary (related to chronic inflammatory lesions). Amyloid is an insoluble protein, and deposition leads to progressive disease and renal failure. Glomeruli are irreversibly damaged by amyloid deposition, leading to decreased filtration and chronic renal disease. Certain strains of mice such as the MRL, New Zealand black, and New Zealand white strains and their hybrids may commonly develop an autoimmune renal failure.

Renal disease also occurs in rabbits. In younger animals, infectious causes are more commonly diagnosed, for example, coliform- or *Pasteurella*-induced pyelonephritis, whereas in older animals the condition has a more degenerative appearance, with fibrosis and mineralization noted. Calcium-predominant uroliths may be found within the renal pelvises as well as within the lower urinary tract, and in severe cases, may induce obstruction.

Transmission

These diseases are not contagious.

Predisposing Factors

Laboratory rats on conventional laboratory diets have a high incidence of chronic renal disease. Nephrosis in conventionally housed rats is evident at 3–6 months of age. Renal changes are delayed and reduced in germ-free rats. Predisposing factors include advancing age; male sex; strain (e.g., a higher incidence is seen in Sprague-Dawley rats); diets high in certain proteins, carbohydrates, and calories or low in potassium; and immunologic characteristics of the strain.

Some strains of hamsters are more susceptible to amyloidosis than are others, and age and female sex are major predisposing factors in this species.

Clinical Signs

Chronic renal disease is usually subclinical and often is only detected at necropsy or when animals present for other conditions, such as gastric stasis in rabbits. In severe cases, usually in older animals, it is a major life-limiting disease. Affected animals progressively lose weight, become inactive, and die. A pronounced proteinuria (mostly albumin) appears in affected rats. Polyuria may appear in hamsters, guinea pigs, chinchillas, rabbits, and mice. Mice with autoimmune nephrosis may also have anemia and generalized edema.

Necropsy Signs

Chronic renal disease is by definition a bilateral nephrosis in which the kidneys may be enlarged in the earlier stages and small in more advanced stages; discolored, brown to pale tan to yellow; nodular with a granular or pitted surface; and have radial, pale striations on cut sections. The capsule may be difficult to peel back from the cortical surface because of multifocal cortical adhesions.

Histologic changes include tubular dilatation with proteinaceous or mineralized casts within the lumen, thickening of the mesangium by protein deposition with synechial formation between the glomerular tufts and Bowman's capsule, interstitial fibrosis with leukocytic infiltrate, and tubular atrophy and regeneration. Glomeruli may become sclerosed and shrunken in advanced disease. In hamsters, guinea pigs, and mice, amyloid is deposited on basement membranes and in the glomerular mesangium. Amyloid may be demonstrated with a differential stain (Congo red) and polarized light (apple green birefringence).

Diagnosis

Diagnosis of nephrosis is based on gross and microscopic lesions as described and on clinical signs. Clinical chemistry (BUN, creatinine) may not be useful in the early stages of the disease. Urinalysis may demonstrate an isosthenuric specific gravity and marked proteinuria.

Treatment

There is no treatment for this condition beyond palliative care. Animals should be provided with supplemental fluids and the diet should be modified. Potassium-binding agents and low-protein/low-potassium diets may offer palliative support, and iron supplementation should be provided if anemia is present. Any underlying disease processes, for example, urolithiasis or infections, should be treated, as appropriate.

Prevention

Ensuring a species-appropriate diet is fed and that the amount of diet fed is not excessive are important preventatives. Ad libitum access to potable water is important for these species to prevent dehydration. Rabbit and rodent salt wheels can be provided to encourage water consumption.

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OXYURIASIS (PINWORMS)

Hosts

Pinworms, host-specific oxyurid nematodes that inhabit the intestinal tract, are common among vertebrate hosts, including several small mammal species. They have not been reported in guinea pigs or chinchillas.

Etiology

Passalurus ambiguus occurs in rabbits, cottontails, and hares. *Syphacia obvelata* occurs in mice and other rodents, including hamsters. *Syphacia muris* occurs in rats and other rodents. *Syphacia mesocriceti* occurs in hamsters. *Aspiculuris tetraptera* occurs in mice and other rodents. *Dentostomella translucida* occurs in gerbils.

Pinworms are commensal, mildly or nonpathogenic, ubiquitous, bacteria-feeding roundworms often seen by the dozens in the lower intestinal tract of rabbits and rodents. Pinworms have a direct life cycle. *Syphacia* spp. have a prepatent period (duration of time from ingestion of ova to the appearance of ova in the feces) of 8–15 days, whereas *Aspiculuris* spp. require approximately 23 days.

Transmission

Hosts are infected by ingesting embryonated ova in feces; fecal-contaminated feed, water, or debris; or through ingestion of ova adhering to the perianal skin (*Syphacia* spp. only). *Aspiculuris* spp. and *Passalurus* spp. ova are passed in the feces; embryonation of *Aspiculuris* spp. ova requires six days outside of the host. *Syphacia* spp. ova on the perianal skin embryonate within a few hours of deposition, and retrograde infection may occur. Pinworm ova are light and are aerosolized easily. Typical sentinel-monitoring programs detect only heavy ova burdens, and infections may remain undetected within a colony.

Predisposing Factors

Animals with diminished resistance are more susceptible to pinworm infections. Intestinal pinworm populations vary with the host's age and sex. In enzootically infected colonies, *Syphacia* spp. numbers plateau in 5- to 6-week-old animals and then diminish as the host ages and develops immunity. *Aspiculuris* spp. populations increase to a plateau when the host reaches approximately 10 weeks of age. Male hosts are generally more heavily parasitized by pinworms than are females, and worm populations vary with the composition of the intestinal microflora and among inbred strains. For example, DBA/2 mice are highly susceptible, whereas C3H mice are more resistant.

Clinical Signs

Clinical signs related directly to oxyuriasis are observed uncommonly even in hosts harboring dozens to hundreds of worms. Reported signs include diminished weight gains, decreased activity, rectal prolapse, and self-mutilation of the tail base from rectal irritation associated with severe *Syphacia* spp. infections. Impaction, intussusception, increased stickiness of fecal pellets, and reproductive depression have also been reported. *Passalurus* spp. nematodes are nonpathogenic for rabbits.

Necropsy Signs

Necropsy signs of pinworm infection are rare and are limited to intussusception and catarrhal enteritis. The small, adult worms are visible in the intestinal contents at the site of gastrointestinal infestation and eggs are typically seen in close association with the mucosa: *Syphacia* spp. in the cecum and colon, *Aspiculuris* spp. and *Passalurus* spp. in the anterior colon and cecum, and *Dentostomella* spp. in the small intestine. Larval forms of mouse pinworms are frequently found at the base of mucosal glands near the rectum. Pinworms are confined to the intestinal lumen (Figure 5.20) except for rare reported cases of penetration through the intestinal epithelium by *Aspiculuris* spp. larvae. Histologically, there may be mild colonic inflammation. Characteristic profiles of the nematodes are seen commonly in the lumen of the cecum or colon when sections of these organs are examined microscopically.

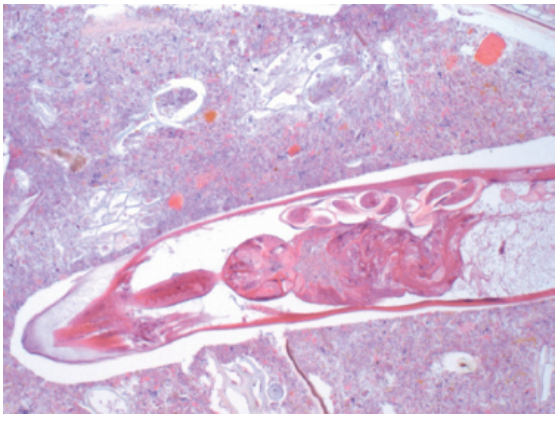


FIGURE 5.20. Photomicrograph of a gravid female pinworm within the colonic lumen of a mouse.

Diagnosis

Diagnosis of oxyuriasis depends on finding the adult nematodes in the small intestine, cecum, or colon; finding adults or ova in the feces; or, in the case of *Syphacia* spp., finding eggs or adult worms on cellophane tape pressed to the perianal skin. *Aspiculuris* spp. and *Passalurus* spp. do not deposit ova around the anus. Exhaust air dust PCR sampling is also an effective means of detecting colony infection.

Adult worms range in length from 1 mm to 1.5 mm for *Syphacia* spp. males to 11 mm for *Passalurus* spp. females. Females are much longer than males for all species. Most are between 2 mm and 4 mm long with a tapered shape and pointed ends, thus the common name pinworms. *S. obvelata* ova are ellipsoidal (banana-shaped), approximately 120–150 µm × 35–50 µm, and somewhat flattened on one side. *Aspiculuris* spp. ova are symmetrical and football-shaped. Adult worms and ova can be seen in fecal smears, but this method has limitations because worms in the cecum and large intestine lay ova in boluses and then die. Ova may be seen in cecal floatation, cecal concentration preparations, fecal flotation, and fecal concentration preparations, as well as in histologic section. Perianal impressions on cellophane tape may be used for *Syphacia* spp. detection. All methods are equally useful for detection of pinworms, although histology may be a more sensitive technique following pinworm eradication.

Treatment

Although numerous treatment regimens have been reported, treatment alone usually results in only a transient elimination of the intestinal nematodes. It is imperative that treatment of the environment occurs concurrently. All chemicals used to treat pinworm infections may induce altered behavioral effects, may alter reproduction, or may induce toxicity in new strains of genetically engineered animals, particularly those with blood–brain barrier defects. For new colonies, it may be prudent to first test these drugs on a small number of animals to ensure safety.

Fenbendazole (a benzimidazole) has been used with success to eliminate pinworms from rabbits and rodents. Diets containing fenbendazole may be irradiated but should not be autoclaved, as the compound is not heat stable. For rabbits, fenbendazole in the feed for five days at either 25 ppm or 50 ppm eliminated internal parasite infestation and was well tolerated by the animals.

In mice and rats, fenbendazole at 150 ppm in the food has continued to be a successful treatment to eradicate pinworms. This chemical is generally used in a "week on–week off" rotation for at least three cycles (i.e., minimum 6-week treatment plan). The addition of fenbendazole may alter feeding intake in rats.

Topical administration of ivermectin in a 0.01% spray solution misted over the animals is reported to be effective at eliminating pinworm infections in mice. No more than 1 mL of this dilute spray should be administered to each animal, and this treatment is not suitable for suckling mice. Topical selamectin at 0.6 or 6.0 mg/kg was reported to be ineffective against pinworm infections in mice and rats.

Piperazine as a 34% solution administered in the water is effective at eliminating pinworms in rabbits as is 2.1 mg/mL in water for mice or rats (for 4–8 weeks). Rabbits are treated on a "week on–week off" basis for at least three cycles.

Prevention

Prevention and eradication of pinworm infection in rabbits and rodents can be extremely difficult. Bedding dusts and wild rodents should be reduced and eliminated. Filter tops should be used, and cages, rooms, and air ducts should be cleaned frequently. Quarantine should be initiated for animals with unknown health histories. Higher fiber diets are reported to reduce worm populations. Two percent peracetic acid or formaldehyde vapor treatments may not kill all pinworm ova in the environment, whereas hydrogen peroxide vapor may be effective at killing some egg forms.

The ovicidal effects of heat and a variety of chemical disinfectants were tested on ova of *S. muris*. Seventy percent ethanol and heating at 80 °C for 30 minutes were the two most effective treatments for killing ova.

Impact on Research

Rats infected with pinworms may weigh 11–12% less than uninfected rats and may not be suitable for nutrition studies because infected rats do not have the growth potential of animals free of parasites. Studies that use organ weight relative to body weight data may introduce systematic error in calculations when infected animals are used. Although they

are generally suspected to be largely nonpathogenic, pinworms may induce myelopoiesis or erythropoiesis and alter other cytokine and immune functions.

Public Health Significance

Humans are a dead-end host for these parasites.

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PARVOVIRUS INFECTIONS

Hosts

Parvoviruses have been identified in mice, rats, hamsters, and rabbits.

Etiology

Parvoviruses are small, nonenveloped, single-stranded DNA viruses that only replicate in rapidly dividing cell populations, such as those found in gut, skin, and lymphoid tissue. Compared with other domestic animals such as dogs and cats, parvoviral infections of rodents spare the gastrointestinal tract, and the disease is generally subclinical. In rabbits, a very mild enteritis has been produced following experimental infection, and the infection is likely subclinical under natural conditions. Therefore, this virus is not clinically important in small mammal pet practice.

Laboratory mice are frequently infected with parvoviruses of two closely related serotypes, mouse minute virus (MMV) and mouse parvovirus (MPV), each representing a family of distinct viral strains. The prime target tissues for viral receptors for both virus types are the small intestine, endothelial cells, and lymphoid tissue. MMV is transmissible to other rodents, particularly hamsters. Infant mice are more permissive hosts to MMV infection than adult mice. A genetically distinct mouse kidney parvovirus also known as mouse chapparvovirus (MuCPV) is a newly identified parvovirus of mice that can cause inclusion body nephropathy and chronic renal failure with fibrosis in severe immunocompromised mice. It has been found in wild, companion, and laboratory mice with worldwide distribution. It is transmitted by fecal–oral and urine–oral routes.

Similarly, numerous strains of rat parvoviruses have been identified to date, including RV, H-1 virus, RPV-1a, minute virus (RMV-1a, -1b, -1c), novel bocaviruses, and so forth. Only RV infection has been associated with clinical signs in rats, whereas the other viruses produce subclinical infections.

Parvoviruses have been identified and characterized in rabbits and hamsters, although this has not been an area of active research in recent years. Based on PCR evaluation, the hamster parvovirus is closely related to the mouse parvovirus MPV-1.

Transmission

Parvoviruses are thought to be transmitted by oral or nasal exposure. Studies evaluating MPV infectivity when transferring embryos, gametes (sperm and oocytes), and ovarian tissue from infected mice demonstrate a high rate of MPV infectivity (up to 68%) in pups following transfer. The viruses can also be transmitted via virus-contaminated mouse tissues, tumor lines, and various biologics. MuCPV can be readily eliminated from colonies by embryo transfer suggesting that vertical transmission is less important for this virus.

Predisposing Factors

Parvoviruses are capable of infecting both juvenile and adult animals and immune competency is not a factor in terms of susceptibility to viral infection, although it may be important in viral clearance and clinical signs.

Clinical Signs

In mice, infection with MPV or MMV is generally subclinical even in immunodeficient animals, but immunomodulatory effects may occur that can interfere with the research objectives. The virus requires mitotically active cells and targets specific tissues by means of viral receptors. Experimental inoculation of newborn mice with MMV resulted in runting and cerebellar hypoplasia. MMV tends to cause a self-limiting infection in which the virus is cleared within approximately 1 month postinfection, whereas MPV may induce a chronic persistent infection. Both MMV and MPV may affect immune function in adult mice, and MPV replicates equally effectively in adult mice. MuCPV may cause significant pathology in immunodeficient mice with characteristic intranuclear inclusion bodies found in renal tubular epithelial cells.

RV infection of rats can cause fetal resorption in pregnant animals, neonatal cerebellar hypoplasia with ataxia, hepatitis, steatorrhea, and jaundice. Hemorrhagic diathesis may be seen in adults, with cerebral and peritesticular hemorrhage; however, clinical signs are usually absent. Dental deformities and mortality have occurred in young hamsters postexposure to Toolan's H-1 virus. Newborn hamsters inoculated with MMV displayed craniofacial lesions, periodontal disease, and death. Dental deformities, domed calvaria, cerebral mineralization, and testicular atrophy have been noted in hamsters exposed to hamster parvovirus, but the disease was confined to suckling and weanling animals.

Necropsy Signs

In mice, MMV infection may induce hemorrhagic lesions following virus-associated damage to endothelium as well as thrombocytopenia. Hepatitis and splenitis have been reported following experimental inoculation of animals with intranuclear inclusion bodies in hepatocytes. RV infection of rats may cause focal hepatitis, periorchitis, and cerebellar hypoplasia with loss of the external granular cell layer.

Diagnosis

Early serologic tests for MPV were based on hemagglutination inhibition assays, which detect antibodies to structural antigens (e.g., capsid proteins). Because the structural antigens for MPV and MMV are markedly different, MPV was not detected by these assays. When immunofluorescence assays were developed for viral identification, which use antigens to nonstructural proteins, MPV was subsequently detected, because the nonstructural proteins are almost identical between MPV and MMV. Antibody typically forms against the structural proteins, and thus humoral immunity to one virus is likely not cross-protective to other strains. MPV may not be detectable from all strains of mice (e.g., DBA). PCR of fecal pellets, mesenteric lymph nodes, and/or environmental samples identifies mice with active infections. MuCPV may be detected from kidney samples, feces or environmental samples. Males may be more sensitive for use in sentinel monitoring. As with MPV, RPV does not share structural antigens with RV, H-1, or RMV.

Serology (MFIA, IFA, and ELISA) and PCR or immunohistochemistry of mesenteric lymph nodes are sensitive means to detect active parvoviral infections. Detection is difficult in cryptic infections. These infections occur when the virus infects a nonactively dividing cell. The virus remains dormant until the cell begins to divide, allowing the virus to be propagated. Seroconversion to rat parvovirus (RV) and Toolan's H-1 virus has been observed in hamsters.

Treatment

There is no treatment for parvovirus infections. MMV and RV infections are generally short-lived and the viruses are cleared from the system, if the animal survives infection. RV may cause persistent infections in young animals born to nonimmune dams. MPV often causes chronic, latent infections.

Because they are nonenveloped, parvoviruses can survive temperature extremes and can only be destroyed in the environment following lengthy exposure to caustic viricides, bleach solutions, and ultraviolet radiation. The most effective procedures for colony elimination are colony depopulation and replacement, or when this is not possible, test and cull approaches followed subsequently by testing specific mice required for breeding programs. Significant efforts should be put into environmental decontamination with detergents and oxidizing disinfectants.

Prevention

Routine use of soiled bedding sentinel systems for virus detection is not an efficient means of detecting parvoviruses in mouse and rat colonies, as viral shedding may be low in infected animals. Care must be used when designing surveillance programs to ensure that sensitive strains of animals are used as sentinels, that they are an appropriate age for infection, and that bedding exposure programs (if used) are set at optimal intervals to maximize detection. Biologics and cell lines must be screened for microbiologic contamination prior to use *in vivo*, although it is unknown whether MuCPV may be transmitted between mice via biologics or cell lines. Use of careful biosecurity and quarantine practices can help to eliminate the virus, including the consistent use of microisolator-type caging for rodents. Other sources of viral entry into a facility, such as wild mice, contaminated feed, biologics and cell lines, and contaminated dust and debris in the air supply

system, should also be considered when investigating an outbreak or designing quality assurance and biosecurity programs for a facility.

Public Health Significance

Rodent and rabbit parvoviruses are not known to affect humans.

Impact on Research

Parvoviruses induce immunomodulatory effects and thus potentially may interfere with many research models, e.g., diabetes, multiple sclerosis, cancer, neurodegenerative disease, infectious disease, and immunologic studies. MMV may suppress bone marrow progenitor cells with chronic infection.

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PASTEURELLA MULTOCIDA INFECTIONS

Hosts

P. multocida induces significant disease in rabbits, but rodents, birds, and farm animals may also be infected by this common animal pathogen. In commercial meat-rabbit breeding operations, pasteurellosis may account for mortalities of up to 15–20% in young fryers (i.e., fattening rabbits).

Etiology

P. multocida is a small, Gram-negative, bipolar staining, coccobacillus bacterium. Colonies on blood agar vary substantially and are considered mucoid, smooth, or rough. Several somatic:capsular serotypes occur in rabbits, with types 3:A, 12:A, and 12:D among the more common. Capsular type A bacteria produce a necrolytic and osteolytic toxin that induces atrophic rhinitis in pigs and rabbits. Within rabbitries and colonies, *P. multocida* isolates are uniform, but between colonies isolates vary.

Significant differences exist in the virulence of various *P. multocida* isolates from rabbits. Some strains predictably cause fatal septicemia, whereas others induce chronic forms of rabbit pasteurellosis such as snuffles.

Transmission

The bacterium is transmitted by direct contact between cagemates, a chronically infected doe and her litter, or between breeding pairs. In breeding operations, the primary means of transmission is between the doe and her kits. Neonates may be infected in the vaginal passage, during nursing, and from contaminated sipper tubes. Maternal antibodies to *P. multocida* persist in young to 6 weeks of age but are not protective. Transmission by respiratory aerosol occurs over short distances, but noninfected rabbits housed in cages adjacent to *Pasteurella* spp. shedders but without direct contact require weeks to months to develop culture-positive nasal infections.

Asymptomatic carriers of *P. multocida* are common, although rabbits used in biomedical research in North America are typically free of *P. multocida*. The organism resides in the nares, paranasal sinuses, tympanic bullae, conjunctiva, vagina, and lungs, where it elicits a minimal inflammatory response.

Predisposing Factors

The ubiquity of asymptomatic carriers and chronically diseased adult rabbits, the ease of transmission to the young by contact, the virulence of the organisms, and preexisting bacterial infections, such as *B. bronchiseptica*, are factors that predispose to pasteurellosis. Environmental factors such as increased ammonia level, temperature fluctuations, drafts, and poor sanitation all contribute to the development of clinical pasteurellosis, as do the stresses of reproduction and older age.

Breed of rabbit and strain of the organism may affect predisposition to infection as well as severity of disease. The pathogenicity of *P. multocida* A : 3 was compared in Flemish giant and New Zealand white rabbits. Flemish giants were much more severely affected than were New Zealand white rabbits, and the score of pneumonia and pleuritis was three times higher in Flemish giants. The pathogenesis of this difference was speculated to be due to greater depression of local immunity in Flemish giants in response to *P. multocida* infections.

Clinical Signs

Clinical signs of *P. multocida* infection range from inapparent, in carrier animals, to peracute death. Septicemia, chronic abscessation, and suppuration in adult rabbits are other signs of the disease. The primary locus of the infection can occur in almost any tissue or organ and spread by the blood to any other tissue or organ, although the nasopharnx and oropharynx are considered the most common primary sites. Abscessation in the liver is rarely caused by *P. multocida*.

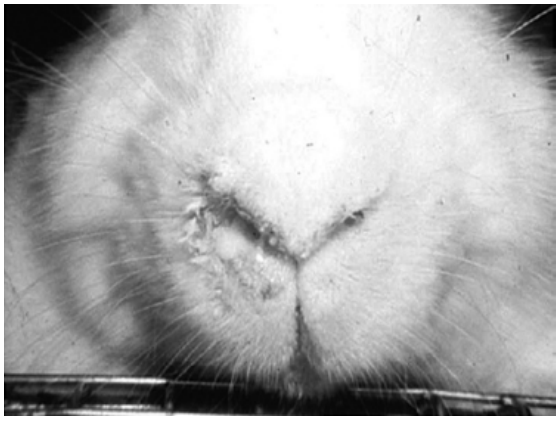


FIGURE 5.21. Pasteurellosis in a rabbit characterized by a mucopurulent rhinitis.

Signs exhibited depend on the site of infection and may include nasal discharge (Figure 5.21), snuffling, runny eyes, torticollis or "wry neck" (head tilt), cutaneous ulceration, subcutaneous swelling, enlarged testes (abscesses), vaginal discharge, infertility, weight loss, and sudden or lingering death. Pneumonia has few clinical signs in rabbits.

Acute enzootic pneumonia is the most common clinical syndrome in young rabbits with *P. multocida* infections, whereas abscesses and suppuration occur more commonly in older animals. Neonates may die from a septicemia. Pulmonary impairment may cause cyanosis of the iris in albino breeds and a short, terminal period of dyspnea.

Necropsy Signs

Gross lesions of *P. multocida* infection may involve one or more of the following: generalized visceral congestion, sanguineous nasal discharge, and focal hemorrhages resulting from septicemia; well-demarcated reddish-gray foci of bronchopneumonia; diffuse fibrinopurulent pleuritis and pneumonia (Figure 5.22); and fibrinopurulent or mucopurulent reactions and abscesses in the meninges and brain (Figure 5.23), middle and inner ear, thoracic and abdominal viscera, nasal passages, subcutaneous tissues, bones, or the reproductive organs. Rabbit pus in a *P. multocida* abscess is characteristically creamy-white and thick.

Turbinate atrophy occurs in rabbits. It has been associated with both A and D types of *P. multocida* but not *B. bronchiseptica* infection.

Diagnosis

Diagnosis of *P. multocida* infection is based on the observation of clinical signs and on the isolation of the causative organism from blood or affected tissues. Nasal swab cultures can be somewhat unreliable as indicators of infection because some carrier animals may be culture-negative and carry the

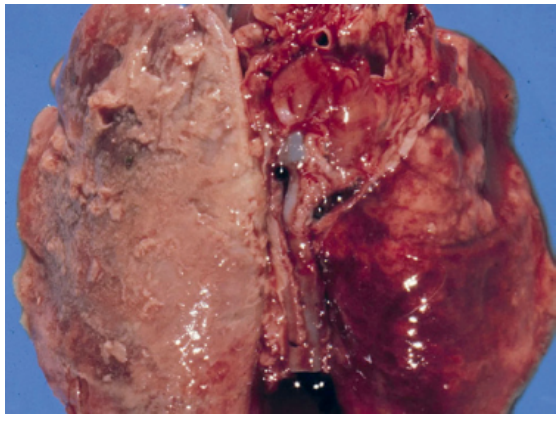


FIGURE 5.22. Lungs from a rabbit infected with *Pasteurella multocida* demonstrating a fibrinopurulent bronchopneumonia.

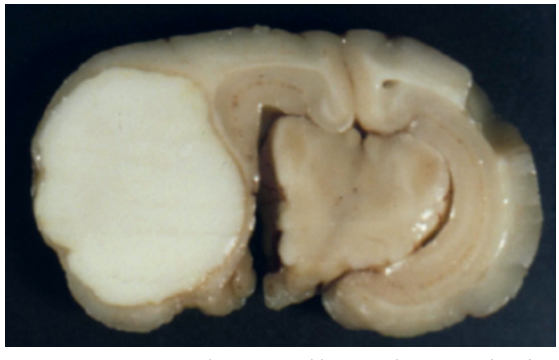


FIGURE 5.23. Brain abscess in a rabbit secondary to *P. multocida* infection.

infection at a site other than the nares, such as the middle ears. In any case, a deep nasal culture taken 2–4 cm into the median aspect of the nares is necessary to detect a nasal or pharyngeal infection. Rabbits may require sedation for this procedure. Finding two sequential negative IgG determinations in sera collected a month apart is useful to confirm a *Pasteurella*-free status in isolated rabbits. Serologic tests may not detect acute infections, whereas culture methods may not detect chronic infections. Both approaches are needed when determining the status of a colony.

Culture of large numbers of animals and culture of sites in addition to the nasal cavities and the oropharynx will help to confirm a carrier state. Purulent processes in rabbits are usually due to *P. multocida* or *S. aureus*. Both grow on blood agar. *P. multocida* is nonhemolytic and produces large, translucent, smooth, or mucoid colonies up to 3–4 mm in diameter. *Staphylococcus* colonies are smaller, dry, opaque, and often hemolytic. Gram staining will provide a final diagnosis. *P. multocida* should also be differentiated from *R. heylii* and *B. bronchiseptica* infections through the use of indole, glucose, and urea cultures.

ELISA tests are also available for serologic monitoring of bacterial status. Skull radiographs are very helpful when trying to determine the extent of disease in chronic infections, such as atrophic rhinitis and otitis media.

Treatment

Although aggressive antibiotic treatment may eliminate the bacterium in acute infections, it is important to be aware that treatment of chronically infected pet rabbits is likely to be palliative. Antibiotics have poor penetration into abscessed lesions, and owners should be warned that treatment will be symptomatic, intermittent, and lifelong.

Antibiotic therapy should be based on culture and sensitivity findings. Enrofloxacin, ciprofloxacin, parenteral procaine penicillin, gentamicin, and trimethoprim–sulfa have all been used with good effect to suppress clinical signs of the disease following a 14- to 21-day course of treatment. Quinolone antibiotics should not be used in young animals, as they may induce arthropathies and they can be irritating when given by SC routes. Owners should always be cautioned to watch for changes in activity, appetite, and fecal output whenever antibiotics are administered to rabbits. It is important to note that there are no vaccines or drugs currently approved for specifically treating pasteurellosis in meat-type rabbits. Segregated-medicated early-weaning methods can be used to eliminate the bacterium from commercial operations, as have been used effectively in pig production facilities.

Removal of environmental irritants such as dusty bedding and moldy hay or straw, provision of a nutritious and appropriate diet, and general attention to routine husbandry and management of animals will go a long way toward minimizing clinical signs of the disease and keeping animals comfortable.

Conjunctivitis can be treated with an appropriate ophthalmic ointment or drop containing gentamicin, ciprofloxacin, or tetracycline. If there is discharge, the nasolacrimal ducts should be flushed with warm saline following administration of a topical anesthetic and using a 21-gauge teflon IV catheter. Ophthalmic ointment can be instilled as a final flush. Careful and gentle cleaning of matted fur surrounding the eye will add to rabbit comfort. Partial ear canal ablation and lateral bulla osteotomy have been used to treat rabbits with significant chronic otitis. Complication rates following surgery remain high, but this may be due to late surgical intervention during the course of the disease in rabbits.

Prevention

Rabbit pasteurellosis is enzootic in most commercial meat rabbitries and in many pet-rabbit breeding facilities, and is difficult to eradicate. Selection of *Pasteurella*-free or *Pasteurella*-resistant stock, repeated culture surveys of rabbits in the colony with culling of affected individuals, and provision

for a 3-week entry quarantine with culture or serologic screening are methods of preventing entry and eliminating the organism from a rabbitry.

High husbandry standards, elimination of ammonia, and stabilization of the environment preclude the development of the more severe forms of the disease in adults. As young animals are susceptible to pulmonary infection, chronically infected does should be culled. Weaning the young at 4 or 5 weeks reduces exposure to the infected mother. Frequent manure removal and good ventilation reduce accumulation of ammonia.

The prophylactic use of sulfaquinoxaline-supplemented water (0.05%) may reduce the incidence of enzootic pneumonia in exposed young until they can be isolated at weaning. Antibiotic eradication schemes have many shortcomings, including the generation of diarrhea, and are no substitute for culling, cleaning, and repopulation with *P. multocida*-free or *P. multocida*-resistant rabbits.

Public Health Significance

Although transmission of a rabbit infection to humans is unlikely, *P. multocida* can cause skin infections, arthritis, meningitis, peritonitis, pneumonia, and septicemia in susceptible humans. Identical serotypes of *P. multocida* can be cultured in poultry, cattle, rabbits, and cats, making cross-species transmission of the bacterium likely in extensive operations where two or more of these species co-exist.

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PEDICULOSIS

Hosts

Lice as a whole have a wide host range, but individual species are host-specific. Mites and lice sometimes occur together on the same host.

Etiology

Lice are flattened obligate parasitic insects, with six legs and no wings. *Polyplax* spp. and *Haemodipsus* spp. are of the suborder Anoplura—sucking lice. *Haemodipsus ventricosis*, the rabbit louse, has a life cycle of 30 days and its ova hatch seven days after being laid. *Polyplax serrata*, the house mouse louse, is a blood-sucking louse and has a life cycle of 13 days. *Polyplax spinulosa*, the spined rat louse, is common in wild rats, has a life cycle of approximately 26 days, and is also a blood-sucking louse. Its ova hatch six days after being laid.

Gliricola spp. and *Gyropus* spp. are of the suborder Mallophaga—biting lice. *Gliricola porcelli*, the slender guinea pig louse, and *Gyropus ovalis*, the oval guinea pig louse, abrade the skin to obtain fluid. Of the species listed, *Gliricola* spp. and *Polyplax* spp. are relatively common, while *Gyropus* spp. and *Haemodipsus* spp. are relatively uncommon.

Transmission

All life cycle phases occur on the host. Ova (nits) are cemented to hair. Transmission of lice is by direct contact with an infected host or bedding. Lice seldom leave a living host.

Predisposing Factors

Animals with decreased resistance or young animals housed in unsanitary conditions may experience more severe infections and clinical consequences than do normal animals.

Clinical Signs

Infection by the rabbit louse, *H. ventricosis*, may cause pruritus, alopecia, weakness, and anemia. The rabbit louse affects dorsolateral areas of the trunk more often than other areas of the body.

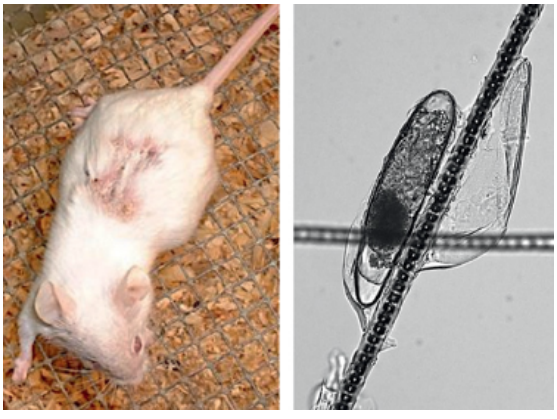


FIGURE 5.24. Multifocal ulcerations and swellings in a mouse infested by *P. serrata* (left). Nits were demonstrated on the pelage of many mice in the affected colony (right).

Infections with *Gliricola* spp. and *Gyropus* spp., the guinea pig lice, are usually benign but can cause scratching, partial alopecia, and scabs, usually around the ears.

Polyplax spp., mouse and rat lice, are found on the neck and body. They may cause debilitation, anemia, scratching, numerous small, scabbed wounds over the side and back, and death (Figure 5.24). *P. serrata* of mice transmits the blood-borne protozoal agent of murine eperythrozoonosis, and *P. spinulosa* of rats transmits the blood-borne protozoan agent of murine haemobartonellosis. Animals without a history of louse infection and no history of receiving a parenteral inoculation of contaminated biological materials should be free of these protozoal infections.

Diagnosis

A hand lens or dissecting microscope is used to observe the pelt for adult or immature ectoparasites, especially the margin of lesions and the nape of the neck. Nits are readily visible on hair shafts. If the animal is dead, direct observation for lice is easier if the pelt is cooled in the refrigerator for 30 minutes, removed for 10 minutes, and then examined with a lens. The parasites migrate from the cool skin toward the warmer hair tips. Placing the suspect pelt on a dark paper within a frame of double-gummed cellophane tape or petroleum jelly will trap the lice and facilitate detection. *Haemodipsus* spp. are 1.2–2.5 mm long and have an oval abdomen. *Polyplax* spp. are slender and are 0.6–1.5 mm long. *Gliricola* spp. have a narrow head and body approximately 1.0–1.5 mm long. *Gyropus* spp. have a wide head and oval abdomen and are 1.0–1.2 mm long.

Treatment

Lice may be killed with the treatments described in the section on acariasis. Elimination of ectoparasites from a room requires treatment, removal of the animals from the room, thorough mechanical scrubbing of equipment and surfaces, and formaldehyde fumigation of equipment and premises. Self-grooming by the rodent host helps in the control of the louse population.

Prevention

Pediculosis is prevented by installing parasite-free stock in a parasite-free facility. Examination for lice during and after quarantine and barrier housing will protect a colony. If lice are a problem elsewhere in a facility, the animals should be quarantined and treated, and the equipment should be cleaned and disinfected. Wild rodents and lagomorphs may have pediculosis and should be excluded from colonies of domestic animals.

Public Health Significance

H. ventricosis is a vector for the transmission of *Francisella tularensis* (tularemia) from rabbits to humans. *Gliricola* spp. and *Gyropus* spp. do not affect humans. *Polyplax* spp. may serve as vectors for rickettsial organisms. Because of their high host specificity, humans are unlikely to acquire pediculosis from laboratory rabbits and rodents.

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PNEUMOCYSTOSIS

Hosts

Pneumocystosis is usually a subclinical pulmonary condition that occurs widely in mammalian species including domestic rodents and domestic rabbits, primates, ungulates, carnivores, and numerous other animal species, including humans. The most relevant clinical disease occurs in immunodeficient mice.

Etiology

Pneumocystis spp. are unicellular fungal organisms that are ubiquitous in the environment. Four basic stages of the organism—trophozoites, precysts, cysts, and intracystic bodies—inhabit the alveoli of infected animals. The cyst forms are 4–6µm in diameter and contain eight crescent-shaped sporozoites. Trophozoites are polymorphic with a

single nucleus and are 1–5 µm in diameter. They adhere tightly to the alveolar wall.

Mouse (*P. murina*) and rat (*P. carinii*)-derived isolates are distinct species and infections are host-specific.

Transmission

The organism is transmitted by the respiratory route or as an aerosol. Because of the ubiquitous nature of this organism, conventional rodents should be envisioned as living in a cloud of *Pneumocystis* spp. spores. They are typically infected as 3- to 4-week-old juveniles. Immunity to the organism develops rapidly, and young animals are initially protected by colostrum antibodies. Virtually all rodents in the 4-to 12-week-old age groups should be considered to be infected and shedding. The organism doesn't cross the placenta, thus cesarean-section rederivation will eliminate the organism.

Predisposing Factors

Subclinical infections with *Pneumocystis* spp. are relatively common in mice and rats. Immunocompetent animals develop a mild subclinical infection that resolves in 5–6 weeks, whereas immunodeficient animals (either natural or acquired) are unable to clear the organism from their respiratory tree and may develop a chronic infection. Thymectomy is not a predisposing factor.

Clinical Signs

Continuous antibiotic therapy, genetic factors, and concurrent viral or bacterial infections frequently play an important role in the incidence of clinical disease. Hunched posture, dyspnea, and wasting have been observed in infected mice.

Necropsy Signs

At necropsy, the lungs appear edematous, pale, and fail to collapse. Diffuse alveolitis, mobilization of alveolar macrophages, and the presence of vacuolated eosinophilic proteinaceous material within alveoli are characteristic microscopic findings. Typical spherical cyst forms may be demonstrated by PAS reactions or silver stains on fixed specimens. Lesions are particularly severe in SCID or athymic nude mice. The organism is thought to be species-specific; thus, interspecies transmission is unlikely to occur.

Other conditions may result in accumulations of foamy or proteinaceous material in the lungs of mice, and because of the long-term implications for colony management, it is important to confirm the diagnosis.

Diagnosis

Examination of methenamine-silver-stained paraffin-embedded sections for trophozoites and cysts and PCR techniques are sensitive means of detecting the organism. Electron microscopy is no more sensitive than histology in detecting clinical infections. Serology is only useful for monitoring immune competent animals.

Treatment

It is important to note that antibiotic treatment controls disease signs but does not eradicate the infection. Because *Pneumocystis* organisms cannot obtain folic acid from the environment and depend on de novo synthesis, trimethoprim–sulfa drug combinations can be used for treatment due to their inhibition of folate metabolism. Trimethoprim–sulfa suspensions (50 mg trimethoprim/250 mg sulfamethoxazole per mL) administered via drinking water is a convenient means to treat affected colonies. The suspension is added at a rate of 15.6 mL/500 mL water bottle. The drug will settle out of solution, and the water bottle must be shaken daily to resuspend the agent. Treatment may be either continuous or following a "three days on–four days off" pattern with regular water being supplied in the off-treatment days. Treatment should be considered to be palliative only.

Prevention

Prevention of pneumocystosis is achieved by purchasing stock known to be free of *Pneumocystis* spp. Once established in a colony, it is difficult to eliminate.

Public Health Significance

Isolates for animals are distinct from human isolates.

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PODODERMATITIS

Hosts

Ulcerative pododermatitis in rabbits, a common condition known as "sore hocks" or bumblefoot, occurs unilaterally or bilaterally on the plantar metatarsal surfaces (footpads of the rear feet) or, less often, on the palmar metacarpal surfaces. A variation of this condition affects guinea pigs, chinchillas, and rats but less frequently than rabbits.

Etiology

The condition is thought to be caused by pressure necrosis of the epidermis, primarily on the plantar metatarsal surfaces of large rabbits housed on hard or wet floors and in large guinea pigs, chinchillas, and rats housed on wire floors or on coarse woodchip bedding or with insufficient amounts of appropriate bedding. Poor hygiene leading to wet cage conditions and contamination of the open wound with urine and feces increases the severity of the lesions, as does obesity.

Predisposing Factors

Factors that predispose to pododermatitis in rabbits include increased body weight as seen in heavy breeds such as the rex, Flemish giant, or checkered giant; reduced plantar fur pad thickness; bruising; obesity, restraint, inanition, or lack of movement in a small cage; and abrasions caused by irregular cage flooring and coarse and irritating bedding. Affected animals should be culled and not used as breeders. The incidence of pododermatitis increases with age and weight (animals >3 kg) and is seen more during hot humid weather, especially in males. It is doubtful that ulcerative pododermatitis is caused or exacerbated by thumping in excessively excitable animals. Rabbits with heavily furred feet, immature animals, or lightweight breeds are affected less frequently.

In rodents, the condition predominantly arises from housing animals on wire-bottom floors with oversized grids or with metal irregularities leading to abrasions; in unsanitary conditions leading to localized infections; or secondary to coarse bedding or insufficient amounts of appropriate bedding. In the latter situation, animals may spend most of their time interacting directly with a hard cage floor if bedding scatters due to insufficient depth as animals move around. Some softwood chip bedding types also release oils that are irritating to the unhaired footpad of these species.

Clinical Signs

The lesion consists of unilateral or bilateral rounded, focal, scab-covered, often hemorrhagic, cutaneous ulcers on the plantar metatarsal or metacarpal surfaces (Figure 5.25). When secondary infection is present, *S. aureus* is often cultured. In addition to these signs, cellulitis, abscessation, and osteomyelitis may be seen in severe cases. Animals may be reluctant to move and may show signs of variable depression, anorexia, refusal to breed, loss of body condition, and even death.

Diagnosis

Clinical signs and predisposing factors provide the diagnosis. The animal should be firmly restrained in a towel wrap during examination of the plantar surfaces to avoid further trauma to the animal and injury to the handler. Chemical restraint is usually not necessary. To enhance accuracy of diagnosis and prognostication, it is recommended that practitioners, animal caregivers, and owners score the foot lesions using a consistent approach (see Figure 5.26, for example).

Treatment

This is a painful condition for animals as it progresses, and treatment should begin as soon as foot swelling and signs of mild erosion are noted. Treatment includes cleansing, toenail trimming, and application of a topical antiseptic or protective cover together with a nonsteroidal anti-inflammatory drug. Frequently, healing is prolonged and complicated by secondary bacterial infection. The prognosis may be poor for complete recovery in animals with intractable pododermatitis, as chronic infection and ulceration may lead to osteomyelitis. An early humane endpoint may be needed following quality-of-life consideration for the affected animal.

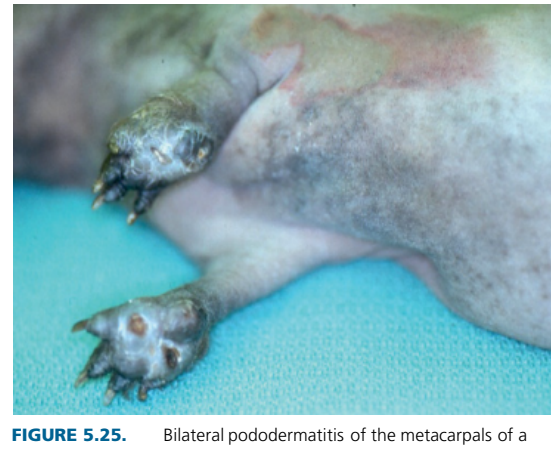
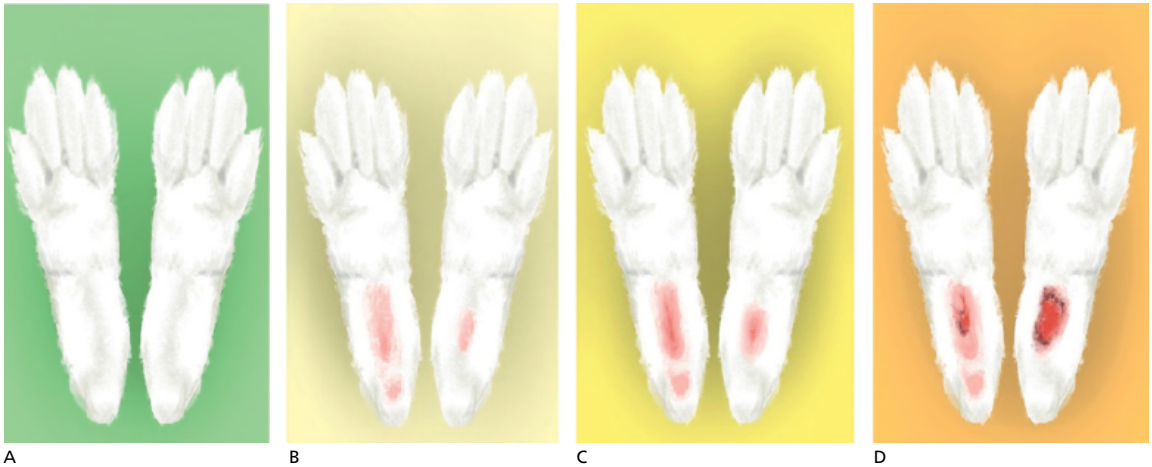


FIGURE 5.25. Bilateral pododermatitis of the metacarpals of a guinea pig.



A B C D

FIGURE 5.26. Scoring system for pododermatitis in rabbits. Routine scoring of pododermatitis can be useful on-farm and elsewhere. The foot lesions are depicted progressing from normal (A), mild loss of fur and reddening of underlying skin (B), early focal abrasions and erosion (C), and chronic ulcerations (D). Modified from Masthoff and Hoy (2019). Illustrations by K. Sokolowski.

In addition to providing soft, dry, clean bedding and a solid cage surface, the affected feet can be soaked in warm Epsom salt solutions to promote healing. In general, bandaging of the extremities is poorly tolerated; however, a light protective dressing in conjunction with a thin layer of antibiotic ointment may be useful. Systemic antibiotics for severe cases, resting boards, and application of topical over-the-counter first aid ointments have been described.

Prevention

Pododermatitis occurs in rabbits housed on both solid and wire floors and in almost any type of cage or confinement device. Prevention is achieved by housing rabbits in clean cages on soft, clean, and dry bedding. Selection of breeders with thick plantar metatarsal fur pads may also help. Eliminating stressful conditions in the environment, providing adequate nutrition and exercise, and guarding against obesity through limit feeding are measures that may help prevent sore hocks. Excessively warm and moist environments may result in a thinner fur coat and a less dense plantar metatarsal hair covering, leaving the foot more susceptible to ulcers and infections.

Rats housed continuously on wire typically may not develop foot lesions until they are at least 6 months of age. Despite this propensity, rats show a strong preference for solid-bottom flooring and the use of wire-bottom cages should be avoided in rodents, whenever possible.

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PREGNANCY TOXEMIA

Hosts

This group of clinically similar diseases occurs in female cattle, rabbits, guinea pigs, hamsters, sheep, goats, nonhuman primates, and humans. Among small mammal species, the disease occurs most frequently in guinea pigs and to a lesser extent in rabbits. Toxemia secondary to hepatic lipidosis and obesity may also be seen in male guinea pigs and rabbits but is obviously not related to pregnancy in these instances.

Etiology

In guinea pigs, the clinical signs are similar, but two distinctly different patterns of disease are seen, a metabolic form and a circulatory form. Both forms occur in sows in advanced pregnancy, and because both syndromes result in similar endpoints, the syndromes may be indistinguishable clinically.

The metabolic form (pregnancy ketosis) of the disease is most common in obese sows carrying four or more fetuses. Adverse stress factors such as poor environment, dietary changes, and low-roughage diets can predispose animals to this condition. The disease can be reproduced experimentally by fasting pregnant (or nonpregnant) guinea pigs, and it can also occur in obese boars and bucks and obese, pregnant does.

The circulatory form of pregnancy toxemia (preeclampsia) is seen in very large sows in advanced pregnancy. The uterine content of guinea pigs in late gestation may represent up to 50% of the body weight of the nonpregnant dam. In this condition, uteroplacental ischemia occurs due to compression of the aorta caudal to the renal vessels by the gravid uterus. This leads to up to a 30% reduction of blood flow to the uterus, infarction of the placenta, and terminal DIC. This syndrome is very similar to preeclampsia in women. Toxemia has been produced experimentally in guinea pigs by banding the uterine arteries. Hypertension, proteinuria, and elevated creatinine levels were observed.

Predisposing Factors

Factors that predispose a guinea pig or rabbit to pregnancy toxemia are multiple. Specific influences include obesity, heredity, change in diet, change in feeding routine, anorexia, large fetal load that may either compress or overextend the vascular supply to the uterus, hypoplasia of vessels supplying the uterus or failure of those vessels to enlarge adequately to supply the primigravid uterus, lack of exercise, and nonspecific environmental stressors. A tendency for more cases to occur during the winter has been noted. Obese boars also develop the metabolic form of the syndrome, though much less frequently than pregnant sows.

Obesity and fasting are also predisposing factors in ketosis in rabbits. The Dutch, Polish, and English breeds have a predisposition to toxemia, as do pregnant, pseudopregnant, and postparturient does, although obese nonpregnant does and bucks may succumb also.

Clinical Signs

The condition usually occurs during the last week of gestation in rabbits and during the last 2–3 weeks of gestation or the first postpartum week in guinea pigs. The condition may be asymptomatic, rapidly fatal, or involve weakness, depression, reluctance to move, incoordination, anorexia, abortion, dyspnea, convulsions, coma, and death over a four- to six-day period. The urine becomes clear (acidic), and proteinuria, ketonuria, and hyperkalemia may develop. This condition is responsible for high fetal wastage in many production guinea pig colonies.

General statements regarding serum calcium, phosphorus, and glucose levels are misleading because of considerable variation among species and stages of the disease within a single species.

Necropsy Signs

Necropsy signs of pregnancy toxemia, when evident, include reduced gastric content, abundant body fat, dead and decomposed fetuses, uterine and placental hemorrhage, adrenal enlargement and hemorrhage, and an enlarged tan liver that is greasy on cut section.

Histologically, hepatic lipidosis, fatty changes in the kidneys and adrenal glands, and the presence of lipids within vessels are typical microscopic findings. Uterine ischemia may be seen in cases of the circulatory form of the disease. Diagnosis is based on clinical, necropsy, and microscopic signs.

Treatment

If toxemia is detected in progress, several unproven treatments can be tried, including administration of lactated Ringer's solution, calcium gluconate, propylene glycol, 5% glucose, and corticosteroids. Use of magnesium sulfate solution to dilate arteries has been attempted in small animals, but results are inconclusive. Guinea pigs under treatment for ketosis frequently die from acute enteritis due, in part, to stress and dysbiosis from inanition and bacterial overgrowth.

Prevention

A critical consideration in preventing toxemia is to avoid fasting animals and to supply fresh water and a nutritious diet. Pregnant guinea pigs should not be subjected to dietary changes or stressors such as transport or drastic changes in environment. Breeding animals should not be permitted to become obese, and weight reduction strategies should be gradual. For this reason, anorexia should always be treated as a serious clinical sign.

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RABBIT VIRAL HEMORRHAGIC DISEASE

Hosts

RHDV causes a peracute infection of European (i.e., domestic) rabbits (*Oryctolagus* spp.). Rodents do not appear to be susceptible. A closely related virus causes a similar hemorrhagic disease syndrome known as the European brown hare syndrome (EBHS). Recent experimental studies and natural outbreaks in wild cottontail rabbits suggest that other lagomorphs also may be susceptible to infection with RHDV. Synonyms for this disease include rabbit plague, rabbit or viral hemorrhagic pneumonia, rabbit viral septicemia, rabbit viral sudden death, and others.

Epidemiology

Though first described in China in 1984, a similar disease, EBHS, was recorded among *Lepus europaeus* on an island near Sweden in 1980. It spread throughout the mainland of southern Sweden in 1981 and by 1982 became enzootic in Denmark. The disease was subsequently reported in Korea in 1985 and in Italy in 1986. The disease emerged in France and Poland in 1988. An outbreak in Mexico started in December of 1988 but was eradicated successfully by 1992. Since that time, the disease has appeared on at least three separate occasions among commercial rabbit farms and exotic mammal exhibits, predominantly in the western United States. The virus has also been reported in commercial meat rabbits and companion rabbits in Canada. In Australia and New Zealand, the virus has been used for biological control of wild rabbits, although virus resistance has emerged following initial introduction.

Etiology

The causative agent is a calicivirus (RNA, single-stranded) that is closely related to the EBHS virus. There are at least two strains in circulation (i.e., RHDV1 and RHDV2) with poor vaccine cross protection between strains. Experimental inoculation studies indicate that the viruses are species-specific and genetically dissimilar. The disease is reportable in both the US and Canada.

Transmission

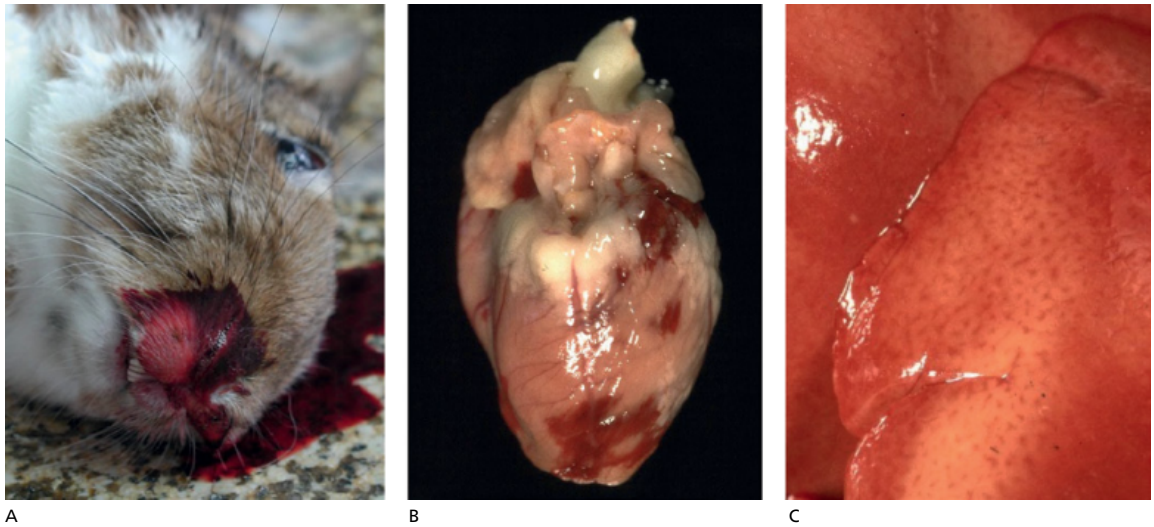
The highly contagious RHDV virus is transmitted horizontally by direct contact with secretions or excretions from infected rabbits or indirectly via aerosol exposure to contaminated fomites, pelts, other rabbit byproducts, and frozen rabbit meat. The 1988–1990 outbreak of RHDV in Mexico was traced to 18 t of frozen rabbit meat imported from China. There is no evidence that it is transmitted by arthropod vectors; however, mechanical means of transmission via birds, rodents, and insects cannot be ruled out. Filtered liver homogenate from infected animals is used experimentally as a source of infectious material because the virus has been difficult to culture *in vitro*. The origin of the virus in recent US and Canadian outbreaks has not been determined.

Predisposing Factors

The virus is highly virulent in rabbits older than 2 months. In enzootic areas, carriers or serologically positive, unvaccinated young rabbits may expose naive adult animals to the disease, thus perpetuating the infection and resulting in eradication failures. Although rabbits younger than 1 month cannot be infected clinically, a small percentage of those between 1 and 2 months old are still susceptible to natural infection. Nutritional inadequacy and environmental stress may increase susceptibility to RHDV. Resistance or natural immunity of young rabbits to experimental infections was not correlated with levels of maternal antibodies, and resistance declined with advancing age.

Clinical Signs

The hallmark of this disease is sudden death without premonitory signs. Morbidity and mortality may be as high as 80–100%. The virus has a short incubation period, from 16 hours to 3 days, followed by high fever (40.5–41 °C [104.9–105.8 °F]) and death within 24 hours. Other signs, not consistently seen, include depression, anorexia, dyspnea, hematuria, vaginal hemorrhage, convulsions, and epistaxis (bleeding from the nose) (Figure 5.27). Because death is acute, affected animals are often in good body condition. The acute form is seen primarily in epizootic areas. Subacute cases with milder symptoms are seen in the later and enzootic stages of an outbreak. Although most animals that survive are resistant to reinfection, some of those that are serologically positive may still carry the virus and shed it intermittently. Chronic nonclinical infection is rare because seroconversion usually affords complete protection, but when present, it is assumed to occur in suckling rabbits.



A B C

FIGURE 5.27. Rabbit hemorrhagic disease virus infections are often associated with sudden death. Animals may present with bleeding from the nose or epistaxis (A). At necropsy, multifocal hemorrhages may be present within certain tissues, such as the pericardium (B). Massive hepatic necrosis also may be seen (C). Courtesy of J.H. Park.

Clinical signs similar to those of RHDV in rabbits have been described in wild hares stricken with the EBHS, which is caused by a related virus.

Necropsy Signs

Blood-tinged nasal discharge, hepatomegaly, splenomegaly, and serosal ecchymoses (Figure 5.27) are typical findings at necropsy. Hepatic necrosis, cryptal necrosis, pulmonary edema and hemorrhage, and lympholysis have been described.

Histologically, there is multifocal to coalescing liver necrosis notable with little, if any, inflammation. Microscopic changes in the spleen include necrosis and microthrombi in small vessels. Microinfarctions due to DIC may be seen scattered throughout the myocardium, kidneys, and other organs. Central nervous system changes, such as microthrombosis, may be found, but they are less common in the CNS than in the other organs.

Diagnosis

Diagnosis of RHDV is based on the characteristic peracute clinical signs and high mortality; gross and histologic lesions, especially necrosis and hemorrhage of the liver and the respiratory system; and detection of virus neutralizing antibodies. Besides ELISA, hemagglutination assay, and PCR of tissue extracts, immunohistochemical staining of frozen and paraffin-embedded tissue sections may be used to demonstrate the disease and confirm the diagnosis.

Treatment

There is no treatment for rabbit RHDV. A multivalent commercial vaccine is available. Nonpharmacologic support may be offered to diseased rabbits; however, the prognosis for recovery is grave.

Prevention

Selection of RHDV-free stock, strict husbandry, quarantine, and serologic screenings are measures to exclude potential sources of infection. During an outbreak, complete depopulation and proper disposal of all infected animals and their fomites with thorough disinfecting of equipment and cages were effective in eliminating the disease and preventing recurrence in Mexico. A multivalent vaccine is available for immunization and protection of companion and commercial meat rabbits in many parts of the world, including Canada and the US.

Because RHDV virus is stable, its elimination from the environment requires decontamination of floors, walls, and fomites using 10% bleach or 3% formalin followed by 2% sodium hydroxide. The premises should be kept empty of animals for 2 weeks during warm weather or 2 months in colder seasons.

Public Health Significance

The lack of evidence of disease in millions of people who have consumed infected rabbit meat and in the large number of farmers, veterinarians, and laboratory technicians who have

been in contact with RHDV viruses indicates that humans are not susceptible to the virus.

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RABIES VIRUS INFECTION

Hosts

Most veterinarians practicing in North America are keenly aware of the potential risk of occurrence of rabies in cats and dogs. Small mammal species such as rabbits and rodents appear to be naturally more resistant to development of rabies infections; however, the disease may occur rarely in these species, particularly if housed outdoors, or in small mammal species adopted from the wild. There are no vaccines approved for use in these species. No human has ever been reported to have developed rabies following a rodent or lagomorph bite. Clients who allow animals to graze outdoors or who shelter their animals outside should be cautioned to protect their animals from feral animal exposures.

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RINGTAIL

Hosts

Tail necrosis or "ringtail" can occur in any rodent species with a glabrous (nonhaired) tail. It is seen in infant mice and rats between 7 and 15 days of age as well as other rodent species, such as juvenile *Mystromys albicaudatus* (white-tailed mice).

Etiology

The disease has been classified as primarily an environmental disorder with the pathogenesis attributed to low humidity and either low or high temperatures, which may result in an aberrant response of the temperature-regulating vessels in the tail of the suckling rodents. Other potential causes cited include a deficiency in essential fatty acids and dehydration, and a primary disorder of cornification in mice has recently been suggested based on a retrospective analysis of histologic and environmental data.

Predisposing Factors

Age and strain are determining factors in the development of ringtail. The incidence in suckling animals is greater than in adults. Long–Evans and Sherman rats are less susceptible than are Wistar and Sprague-Dawley rats. Additionally, conditions that cause lower ambient humidity such as occurs with wire cages, hygroscopic bedding, and excessive air flow rates, predispose animals to ringtail. In the Northern Hemisphere, ringtail is seen most often between November and April, when facilities are artificially heated and interior humidity drops. Nutrient deficiencies, including lack of essential fatty acids in the diet of lactating dams, may predispose infants to ringtail, which can be further exacerbated by low ambient humidity.

Clinical Signs

Animals with mild clinical signs have hyperemic tails with few if any annulations and they usually recover uneventfully. In moderately affected cases, the animals are left with permanent annular constrictions on their tails. In severe cases, the tails become dry and necrotic and slough. The stumps will heal without complications. Affected rats usually have no other apparent clinical or metabolic abnormalities or signs of discomfort.

Diagnosis

Recognition of clinical signs and knowledge of husbandry practices and experimental protocol are helpful in making a diagnosis. Ringtail lesions present as edema, inflammation, and possibly necrosis. These can cause the tail distal to the lesion to slough, leaving a stubby, short tail.

Treatment

Specific treatment for ringtail is usually not necessary as long as all possible predisposing factors are corrected and the animals are housed with clean bedding and fed a balanced diet. Lanolin has been used as a topical ointment to prevent progression of ringtail in rat pups diagnosed early in the course of the condition. Preventing other diseases and environmental stresses from compromising the overall health and immune status of the animal is an important measure in promoting healing and an uneventful recovery.

Prevention

In some instances, ringtail can be prevented by providing a solid-bottom plastic cage with both adequate bedding and nesting material. Use of microisolator caging tops will increase local cage humidity by 5–10% compared with room humidity and may help to prevent the condition. In most cases prevention depends on maintaining the relative humidity of the room at approximately 50% or higher. Nutritional requirements, including essential fatty acid levels, should be met.

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RODENTIBACTER COMPLEX INFECTIONS

Hosts

Mice and rats are susceptible to infections and clinical disease caused by *Rodentibacter* complex bacteria, which are distributed worldwide in conventional and barrier colonies. *Rodentibacter* complex species have been isolated from a variety of hosts, including Syrian hamsters and guinea pigs, but infections in these species are typically incidental and nonclinical and they are not discussed further. This is generally not a disease of major concern in pet rodents.

Etiology

Rodentibacter complex refers to a number of Gram-negative, nonmotile, 1–2 µm long, pleomorphic coccobacilli that are weakly pathogenic, opportunistic invaders. These bacteria were previously classified as part of the *Pasteurella–Haemophilus–Actinobacillus* complex (i.e., *R. heylii* subsp.). The prevalence of infection is high in wild rodents.

Transmission

Rodentibacter complex species often exists in a latent, carrier state in the upper respiratory tract and uterus and are considered part of the normal gut flora of rodents. They may be disseminated by respiratory aerosol or fecal contamination, biting, licking, and intrauterine contamination. Typically, in enzootically infected colonies, nasopharyngeal colonization of laboratory rodents occurs around the time of weaning.

Predisposing Factors

With the proliferation and increased use of immunocompromised and genetically engineered mice, opportunistic infections with bacteria such as *Rodentibacter* complex have emerged as significant problems in some research facilities. Because *Rodentibacter* complex are opportunistic pathogens, circumstances that decrease the host's resistance, particularly other infections, may precipitate clinical disease. *Rodentibacter* complex in conjunction with Sendai virus infection of mice results in fatal pneumonia, and *Rodentibacter* complex species may complicate *M. pulmonis* infection or other infections in rats and mice.

Clinical Signs

Characteristically, morbidity and mortality are low. *Rodentibacter* complex species are widespread as latent infections, but the bacteria cause clinical disease only sporadically. Signs associated with *Rodentibacter* complex infection include chattering, labored respiration, weight loss, skin abscesses, head tilt, Harderian gland abscesses, conjunctivitis (Figure 5.28), panophthalmitis, mastitis, infertility, bulbourethral

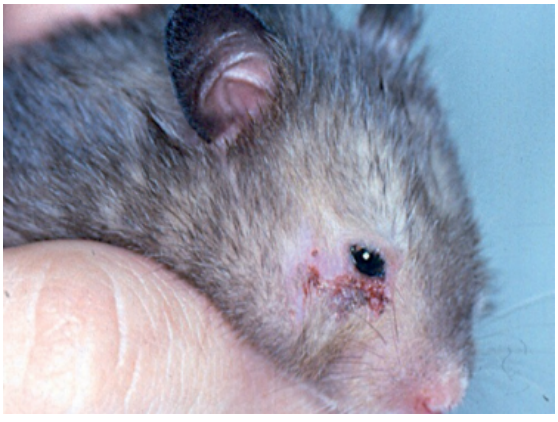


FIGURE 5.28. Conjunctivitis in a hamster. This condition may be seen with *Rodentibacter* complex infections.

gland infections, abortions, internal and subcutaneous abscesses, and death.

Necropsy Signs

The manifestations of infection and the target organs vary, but chronic suppurative bronchopneumonia (frequently as a co-pathogen), chronic endometritis, otitis media, chronic suppurative mastitis, preputial gland abscesses, and conjunctivitis are commonly seen. The muscles of mastication may be infected with the bacteria in young pups, leading to anorexia and death. Lesions are especially common in athymic nude mice and infection may lead to chronic wasting in these animals.

Rats may have a severe, multifocal-to-coalescing, acute-to-subacute, necrotizing-to-fibrinous bronchopneumonia, which must be differentiated from pneumonias caused by *Streptococcus* spp. and *Corynebacterium* spp.

Diagnosis

A definitive diagnosis of *Rodentibacter* complex infection is established through recovery of the organism on culture. After 24 hours of aerobic incubation at 37 °C on blood agar, the colonies are small (1 mm), circular, convex, smooth, and surrounded by a zone of slight greenish discoloration. An ELISA diagnostic test has been helpful in detecting *Rodentibacter* complex infections in mice and specific PCR assays are also available.

Treatment

Enrofloxacin given subcutaneously or in the drinking water was superior to tetracycline in attempts to eliminate *Rodentibacter* complex from oropharyngeal and gastrointestinal sites in mice. Large-scale embryo transfer rederivation may be necessary for breeding colonies of mice with associated bacterial problems. The agents do not survive for long outside the host and widespread environmental decontamination is not necessary. Cesarean section may be used to eliminate the organisms from an infected colony.

Prevention

Elimination of murine respiratory infection from a colony requires a known disease-free stock placed into a clean and barrier-sustained colony. Newly arrived animals should be quarantined until their microbial status has been determined. Cesarean derivation should be done with the knowledge that *Rodentibacter* complex are common uterine inhabitants, as is *M. pulmonis*. The bacteria are most efficiently transmitted by direct contact, and dirty bedding sentinel systems may not be sensitive enough in all cases to detect them. Soiled bedding sentinel-monitoring systems are not robust for detection of this agent.

Public Health Significance

Rodentibacter complex can infect humans, but rodent-to-human transmission is rarely reported. In one recent report, *Rodentibacter* complex was transmitted by a hamster bite to a child undergoing dialysis, inducing peritonitis. Humans may be inadvertent sources of infection for barrier-sustained rodents.

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ROTAVIRUS INFECTIONS

Hosts

Rotaviruses are species-specific enveloped RNA viruses that produce significant intestinal disease in a variety of young hosts, including mice (epizootic diarrhea of infant mice [EDIM]), rats (infectious diarrhea of infant rats [IDIR]), rabbits, calves, and humans. Mouse, rat, and rabbit rotavirus infections are common in wild and domesticated animals around the world.

Etiology

Rotaviruses are 60–80 nm in diameter, contain double-stranded RNA, are nonenveloped, and have capsomers on the surface. Rotaviruses are placed in lettered groups (A, B, C, D, etc.) based on genetic relatedness. Group A rotaviruses cause EDIM, diarrhea in rabbits, and acute gastroenteritis in human infants during the winter months. One of the group B viruses causes diarrhea in infant rats. The viruses cause an inhibition of intestinal absorptive mechanisms through epithelial damage and transport system blocking. Concurrent infection with EDIM and MHV produces a disease that resembles what was once described as lethal intestinal viral infection of mice (LIVIM). Similarly, concurrent infection with enterotoxigenic E. coli increases the severity of rotaviral disease.

Postexposure, the virus may replicate in enterocytes throughout the intestinal tract and may escape the intestine to infect extraintestinal tissues. Manifestations of the disease are most common in the small intestine, but histologic evidence of infection has been noted on occasion in other tissues in rats.

Previous infection by EDIM may affect response of mice to human rotavirus challenges during vaccine efficacy testing thus uninfected animals are preferred for research settings.

Transmission

The viruses of EDIM and IDIR are transmitted predominantly by oral–fecal contamination. In all species, the disease is highly contagious. Animals surviving the clinical disease shed the virus for weeks. The filter cover concept was introduced initially to prevent transmission of rotaviruses among susceptible mice. Mouse rotaviruses are not infectious for rats. Little is known about the transmission of rotavirus infection in rabbits; however, lapine rotavirus species have been detected from children with diarrhea and bovine rotavirus species have been isolated from wild rats.

Predisposing Factors

Clinically apparent diarrheal disease is seen in mice and rats up to 12 or 13 days of age, and it is more severe in mice born to primiparous females. Older animals may be susceptible to rotaviral infections and may shed the virus in large quantities following infection, but they rarely exhibit evidence of clinical disease. The increased susceptibility of neonatal animals to clinical disease appears to be due in part to the reduced kinetic rate of enterocyte turnover in very young animals. Neonatal animals are unable to replace these epithelial cells fast enough, resulting in collapse of villi and diarrhea.

Clinical Signs

EDIM and IDIR are diarrheal diseases of high morbidity and low mortality. Affected suckling mice and rats have watery, yellow diarrhea, and steatorrhea due to malabsorption, but infants continue to nurse and have a milk-filled stomach that is visible through the ventral abdominal wall (milk spot). Sometimes constipation is seen during the convalescent stages.

In rats, diarrhea is usually seen in 8- to 12-day-old pups. The diarrhea persists for 5–6 days and may be associated with erythema, cracking, and bleeding of the perianal skin. Although affected rodents continue to eat, they do not grow normally, and stunted growth is a common sequela. Weaning percentage (percentage of young weaned compared with litter size at birth) may be slightly reduced. When weaned, the young are somewhat underweight for their age. Primary rotaviral infections rarely produce diarrhea in rabbits, but they may play a role in the enteritis complex in this species.

Necropsy Signs

The stomach of the affected mouse is usually filled with milk, unlike sucklings with MHV infection. The gastrointestinal tract of the affected mouse, rabbit, or rat may appear normal or be distended with gas and watery, yellow feces.

In the small intestine, rotaviruses replicate selectively in enterocytes lining the distal tips of villi. In suckling mice, villous atrophy and vacuolation of enterocytes occur during the course of the disease but without the syncytial giant cell formation seen frequently in coronaviral enteritides.

Rats, like pigs with rotaviral infections, develop villous epithelial syncytial cell aggregations, particularly in the distal one-third of the small intestine. Numerous viral particles can be seen with electron microscopy in syncytial cells.

Serologic surveys of commercial rabbitries suggest that the virus is enzootic in conventional animals. Histologic alterations following infection may be seen in rabbits as old as 11 months.

Diagnosis

A diagnosis of rotaviral infection is usually made on the basis of clinical signs, case history, and histologic findings. Electron microscopy of negatively stained specimens prepared from diarrheic feces has been used to diagnose rotaviral infections. ELISA, PCR, and immunofluorescence assays are also available commercially.

Treatment

Little can be done to treat EDIM or IDIR; however, supportive treatment of rabbits and rodents with diarrhea may be indicated.

Prevention

Selection of disease-free stock and the use of cage filter covers (i.e., microisolator cages) will reduce or prevent outbreaks of EDIM. Barrier housing will markedly reduce chances of new infections if good biosecurity practices are in place.

Public Health Significance

Mouse rotaviruses are not thought to affect humans. Rat rotaviruses may be zoonotic and neonatal rats are susceptible to human rotavirus infection.

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SALMONELLOSIS

Hosts

Salmonella spp. are widespread in nature and affect a broad range of vertebrates. The agent is not common in companion rabbits and rodents and is rare in research colonies, but may commonly be found in colonies of feeder mice. Guinea pigs are highly susceptible and develop severe clinical disease; mice are also susceptible and may carry subclinical infections for long periods. Rabbits, chinchillas, hamsters, rats, and gerbils are infected less often, but severe outbreaks have occurred in each species.

Etiology

Salmonella typhimurium and *S. Enteritidis* are the pathogenic species most often isolated from laboratory animals, but many other species of *Salmonella* spp. of equal or lesser pathogenicity have been cultured and typed.

Transmission

Transmission is by the fecal–oral route through ingestion of feces, feces-contaminated feed, or bedding. The conjunctiva is a portal of entry in guinea pigs and probably other species. *Salmonella* spp. frequently exist in a subclinical carrier state in the intestinal tract and are continually shed into the environment, making elimination of infection difficult. Control is made even more difficult because of the ability of *Salmonella* spp. to survive in the environment. Because of good hygienic management and barrier housing, *Salmonella* spp. infections are seen rarely in research facilities.

An outbreak of *S. typhimurium* infections was reported in a commercial rabbitry in New South Wales that resulted in serious economic loss. The source of infection was believed to be local farm hay of poor quality that was used in nest boxes of kindling does. Commercial rabbits and chinchillas are frequently exposed to *Salmonella* spp. in the feed. In another study, a *Salmonella* Group D infection was thought to have spread from cockroaches to gerbils via mosquitoes and a contaminated filarial inoculum.

Predisposing Factors

Among predisposing factors increasing susceptibility to salmonellosis are youth or old age, stress of pregnancy, nutritional deficiencies, concomitant diseases, genetic predisposition, serotype of organism involved, and environmental and experimental stresses. Guinea pigs are highly susceptible in the winter, at parturition, and at weaning. C57BL/6, DBA/1, and BALB/c mice are considered among the more susceptible mouse strains.

Clinical Signs

Salmonellosis in laboratory animals is an enteric and systemic infection that may be enzootic or epizootic. Sporadic outbreaks with high mortality are the rule in guinea pig and chinchilla colonies and rabbitries, but in smaller rodents clinical signs are usually inapparent.

Specific signs, when present, include anorexia, rapid deterioration, rough hair coat, pyrexia, weight loss, light-colored soft feces, conjunctivitis, ocular discharge, small litters, lethargy, dyspnea, abortions, and sporadic deaths, particularly of pregnant dams in the late stages of pregnancy. Rats in one infected colony had no sign other than soft feces.

Necropsy Signs

Lesions of acute salmonellosis include enlargement, congestion, and focal necrosis of the liver, spleen, lymphoid tissues, and intestine. The gut may contain decreased contents and increased amounts of gas and fluid. Pregnant animals may have necrotic metritis.

In subacute or chronic cases the spleen may be enlarged, the liver and gut may be hyperemic, and necrotic foci may be prominent in the viscera. Enlarged and prominent Peyer's patches may be seen throughout the ileal subserosa.

Microscopically, vasculitis and thrombosis are seen in hamsters. Foci of necrosis surrounded by mononuclear cell infiltrates occur in the viscera along with a suppurative lymphadenitis.

Diagnosis

Although necropsy signs may be suggestive of salmonellosis, cultures of the mesenteric lymph nodes, conjunctiva, feces, cecum, or freshly aborted material (if available) are methods of choice for confirming an outbreak or a carrier state of this condition. The agents do not hydrolyze urea and usually do not use lactose. Media may include Gram-negative, selenite, or tetrathionate brilliant green broth to enhance growth of *Salmonella* spp. from fecal samples. A battery of additional biochemical tests can be used to identify further suspect colonies in culture. Suspected *Salmonella* spp. isolates must be confirmed by serotyping because several nonpathogenic enteric bacteria may have similar biochemical reactions. A final determination of serotype is usually performed in a reference laboratory.

Treatment

Treatment of salmonellosis may suppress an epizootic to an enzootic infection, but elimination of carriers is difficult. Because of the major public health concern, colonies infected with *Salmonella* spp. usually should be eliminated, premises sanitized, and proven clean animals used for restocking. Infection of valuable rodents by minimally pathogenic strains of *Salmonella* spp. may be controlled or eliminated by intense culture, isolation, and treatment. *Salmonella* spp. serovars of low virulence may disappear spontaneously without treatment from colonies or other populations. This is more likely to occur in well-maintained barrier facilities.

A therapeutic regimen that has been followed with some success is the addition of oxytetracycline to the drinking water at 10 g/L for 10 days or 250 mg/kg body weight per day. Treated mice were isolated, the remainder of the colony euthanatized, the room disinfected, and first litters monitored for *Salmonella* spp.

Prevention

Rigid, high husbandry standards and screening of new arrivals and resident populations of other species, especially dogs, nonhuman primates, and animal care personnel, will reduce the possibility of outbreaks. Birds, wild rodents, and contaminated feed must be excluded from the facility. Elimination of infection from conventional colonies by treatment is extremely difficult; euthanizing affected animals, disinfecting, and restocking may be more practical.

Public Health Significance

Salmonellosis occurs in humans and can be contracted from, or given to, pet and laboratory animals. Clients and staff should be instructed in proper hygiene when handling small mammal pets or research animals, including rigid post handling hand-washing practices. Within breeding, pet store, and distribution operations, *Salmonella* spp. can be cultured from cages, food, and bedding, emphasizing the need for environmental control if the bacteria are found and strict hygiene control measures to minimize the spread of infection to other susceptible species (e.g., reptiles, dogs, and cats). Routine culturing of pet feces is not warranted but may be advisable in households with immunocompromised individuals or whenever *Salmonella* spp. is cultured from a symptomatic client family member. Several outbreaks of salmonellosis have also been linked to consumption of undercooked rabbit meat contaminated with *Salmonella* spp. bacteria. Rabbit meat must be thoroughly cooked to avoid foodborne disease outbreaks.

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SENDAI VIRUS INFECTIONS

Hosts

Mice, rats, hamsters, guinea pigs, and pigs are hosts for Sendai virus infection. Chinchillas can be infected experimentally with the virus, while gerbils appear to be resistant. Suckling and weanling mice are most commonly and seriously affected. Although viral multiplication is largely limited to the nasal epithelium, laboratory rabbits are also susceptible to Sendai virus infection. Historically in North America, Sendai virus infections caused some of the most significant diseases of laboratory rodents. The disease remains enzootic in research mice in many parts of the world and is highly prevalent in wild and companion rodents.

Etiology

Sendai virus, an RNA virus of the family Paramyxoviridae, genus *Paramyxovirus*, is also known as parainfluenza type 1. Many viruses in the paramyxovirus-parainfluenza group share common antigens. Clinical disease due to Sendai virus is often complicated by mycoplasmal and bacterial infections.

Following aerosol exposure, Sendai virus replicates in respiratory epithelial cells of the nasal passages, trachea, and bronchi, and, depending on various factors (including strain of mice), virus may also replicate in type II pneumocytes. In nude mice, Sendai virus replicates in both type 1 and type II pneumocytes. Intranuclear inclusions have been observed in bronchial epithelium of infected nude mice.

Transmission

Natural infection occurs via respiratory transmission, and passage may be by direct contact, contaminated fomites or tissues, or respiratory aerosol. The disease is extremely contagious. Acutely infected weanling mice (4–6 weeks of age) provide the principal reservoir for transmission in enzootically infected colonies. Disease-free or SPF animals are highly susceptible to infection.

Predisposing Factors

Some inbred mouse strains (129/J and DBA/2) are very susceptible to Sendai virus infection, but other strains (C57BL/6 and SJL) and random-bred mice are moderately resistant. DBA/2 mice are immunocompetent but have a delayed immune response following infection, which permits the virus to become established in the lower respiratory tract. A subsequent vigorous immune response induces significant host tissue damage.

Concurrent *R. heylii*, *C. kutscheri*, and *M. pulmonis* infections greatly increase morbidity and mortality. In susceptible colonies, the disease is overt and epizootic especially if concurrent diseases produce a synergism. An inapparent enzootic form of disease is seen when most dams have been infected and pass maternal antibodies to their young.

Clinical Signs

In enzootically infected colonies, newborn mice are passively protected by maternal antibody until they are 4–6 weeks of age, at which time they become infected and develop an acquired immunity that is probably lifelong. Because adults in enzootically infected colonies have acquired immunity, they rarely show disease. Frequently, the disease is subclinical in weanling mice. Sendai virus infections are nearly always subclinical in rats, hamsters, guinea pigs, and rabbits. Clinical signs of an acute infection in susceptible animals include rough hair coat, chattering, weight loss, dyspnea, decreased breeding efficiency, and variable mortality.

Epizootic disease occurs when animals in an uninfected colony encounter Sendai virus infection. In this case, any and all animals may show clinical signs. There may be high mortality with many sick animals among sucklings. After several weeks of epizootic disease, an enzootic pattern ensues and persists as long as susceptible animals are present; usually weanlings or newly introduced naive or nonimmune mice are susceptible. Athymic mice and other immunodeficient mouse strains are highly susceptible and develop a persistent infection with wasting.

Necropsy Signs

In many animals, rhinitis will be the only visible sign of infection. Acute bronchopneumonia is grossly evident as plum-colored lungs with anteroventral consolidation.

The virus preferentially targets airways and necrotizing bronchiolitis is a classic lesion. Proliferation with or without destruction of bronchiolar epithelium, increased cellularity of alveolar septa, proteinaceous exudation, and the presence of alveolar macrophages and neutrophils in bronchioles and alveoli are frequent findings during the acute phase of the disease. The sloughing of virus-infected bronchiolar epithelial cells corresponds with the appearance of detectable antibody. During the regenerative phase, there is hyperplasia of type II pneumocytes lining airways, with fibrosis, thickening, and mononuclear cell infiltration in alveolar septa. Lesions in airways and alveoli are particularly extensive in athymic and SCID mice.

Diagnosis

Consideration of the species, strain, and age of animals involved and of the clinical, necropsy, and characteristic histologic lesions permits a provisional diagnosis of Sendai virus infection. Serology (MFIA, IFA, and ELISA) assays are available and PCR can be used on symptomatic animals.

Sendai virus can usually be recovered from the lower respiratory tract from 6 to 8 days postinoculation. The elimination of the virus normally coincides with the appearance of detectable Sendai virus antibody in the peripheral blood. Serologic tests are not useful for many immune-deficient mouse strains.

Antigens shared among parainfluenza viruses confuse diagnostic serology efforts. Parainfluenza virus 3 (PI-3) may infect guinea pigs giving false positive results in ELISA serologic tests for Sendai virus (PI-1).

Animals vaccinated with live attenuated or killed vaccines develop titers that may be impossible to distinguish from titers associated with the naturally occurring disease. Inoculation of suspect materials into cell cultures can be used to diagnose Sendai virus infection before antibodies appear and suppress active infection.

Prevention

Prevention of the highly contagious but usually subclinical Sendai virus infection involves selection of rodents from a Sendai-free source and continual seromonitoring of the colony. Because young, recently weaned hamsters, mice, rats, rabbits, and guinea pigs constitute a reservoir population in which the infection maintains itself, the elimination of such young and the exclusion of additional young for 1–2 months may stop an outbreak. Commercial producers successfully use this method to eliminate Sendai virus from breeding colonies.

Previously, a killed vaccine of duck embryo origin was available commercially. The vaccine was prepared in 50-dose vials, and 0.1 mL of the vaccine given intraperitoneally provided approximately 7 months of protection. Others have successfully vaccinated with a temperature-sensitive mutant. Embryo transfer successfully eliminated Sendai virus from infected colonies. There is no evidence of transplacental infection with Sendai virus.

Effect on Research

Researchers should be apprised that a variety of physiologic functions are altered by concurrent Sendai virus infection, for example, depression of cell-mediated immunity, blast cell transformation, phagocytosis, and decreased intrapulmonary anti-bacterial activity. The disease generally has a major impact on animals used in immunologic research, transplantation, and pulmonary carcinogenesis studies.

In animal facilities where the virus is enzootic, it is advisable to purchase vaccinated or older animals, that is, 6 weeks old versus 3 weeks old, when possible. Older animals of susceptible strains have lower mortality and clinical disease is milder.

Public Health Significance

Sendai virus is antigenically related to human parainfluenza virus-1. Although the virus replicates productively in the upper and lower respiratory tracts of several nonhuman primate species, it has not been demonstrated to infect humans spontaneously.

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SPIRONUCLEOSIS

Hosts

The enteric flagellate *Spironucleus muris* infects mice, rats, hamsters, and wild rodents. Clinical disease is seen only in weanling, stressed, immune-suppressed, or inbred mice.

Etiology

S. muris is an opportunistic pathogen of laboratory mice, and occasionally outbreaks of diarrhea with weight loss occur. Co-infection with organisms such as *Giardia* spp. or intestinal viruses or dietary changes may precipitate diarrhea, particularly in young animals. *Spironucleus* trophozoites reside primarily in the intervillar spaces and crypts of the upper small intestine. When associated with disease, blunting of villi, hyperplasia of crypt epithelium, and hypercellularity in the lamina propria, mononuclear cells predominating, are typical pathologic findings. In a morphologic study of kinetics of mucosal turnover of the small intestine in mice chronically infected with *Giardia muris* and *S. muris*, the enterocyte turnover was twice the rate in infected compared with uninfected mice.

The torpedo-shaped trophozoites (2–3 µm × 20–25 µm, flagella included) have two anterior nuclei and eight flagella (two posterior and six anterior). Small, oval cysts (5 µm) have a banded "Easter egg" appearance. The direct life cycle is incompletely known. Resistant cysts survive stomach passage. The prepatent period is 2–3 days. *Spironucleus* spp. feeds on bacteria, probably lactobacilli. It has been proposed that *Spironucleus* spp. can be divided into two main groups. One group is infective for mice and golden hamsters, while the second group is exclusively infective for rats. This conclusion was based on interspecies cyst transfer studies.

Transmission

The environmentally resistant cyst of *S. muris* facilitates transmission by the fecal–oral route. Young and athymic nude mice pass larger numbers of cysts than do adults and other strains of mice.

Predisposing Factors

Susceptibility to *S. muris* infection varies with factors that raise or lower resistance. Co-infection with enterotropic strains of MHV is common. Inbred strains such as C3H, NZW, and DBA/2 and the athymic nude mouse are very susceptible. Mice of both sexes between 3 and 8 weeks of age have the highest levels of clinical infection. Specific stressors include irradiation, steroid administration, crowding, poor nutrition, recent surgery, and chilling. A mild increase in the ambient temperature to 75–80 °F (27 °C) has reduced mortality. *S. muris* inhibits macrophage activity and may act synergistically with bacteria to cause disease.

Clinical Signs

Spironucleosis is an acute, chronic, or latent disease, depending on predisposing factors and duration of infection. The acute disease is characterized by a hunched posture, depression, dehydration, a rough, dull hair coat, distended abdomen, and often a soft, sticky stool. Death at the peak of an outbreak occurs 1–4 days following the onset of clinical signs, and mortality rates may approach 50%. Older mice have a marked variation in signs. Many have no clinical signs. Some may show progressive wasting, listlessness, and sporadic death.

Necropsy Signs

The common necropsy finding is an anterior small intestine grossly distended with a bubbly froth, giving the appearance of postmortem autolysis. The froth may be variably colored but rarely contains blood. The duodenum and anterior jejunum are affected grossly. Other findings may include diarrhea, an enlargement and thickening of the wall of the duodenum, enlarged mesenteric lymph nodes, ascites, and splenic and thymic atrophy.

Histopathologic signs are those of acute catarrhal enteritis or chronic mucosal hyperplasia with minimal mononuclear cell infiltration. Reduction in height of villi, epithelial desquamation, lymphocytic infiltration, villous edema, and the presence of organisms deep in the crypts between villi (Figure 5.29) are common microscopic findings.

Diagnosis

Spironucleus spp. infections may not be detected with soiled bedding sentinel systems. Cysts and trophozoites may be seen on microscopic examination of direct smears of duodenal contents or in fixed and stained sections; however, histology may be more sensitive for detection than direct examination of smears because the trophozoites autolyze rapidly in unfixed preparations. Trophozoites can be seen in hematoxylin and eosin-stained or PAS-reaction sections distending the lumen of the crypts of Lieberkuhn in the duodenum (mice and hamsters) and in the pylorus (rats). Alternatively, PCR tests may be used to detect the organism in tissues. Cysts, which may be quantitated, are better seen with iodine staining or phase

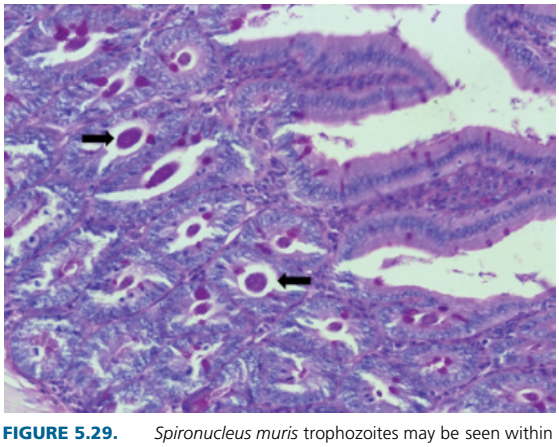


FIGURE 5.29. *Spironucleus muris* trophozoites may be seen within clusters (arrows) within intestinal crypts of mice (PAS stain).

contrast optics. In direct smears diluted in an isotonic saline solution, the trophozoites of *S. muris* have a fast, forward, erratic movement, whereas the larger *Giardia* spp. trophozoites are spoon- or half-moon-shaped and have a rolling motion in a liquid environment.

Treatment

When the antiprotozoal agent dimetridazole was given in the drinking water (0.04–0.1%), mortality was reduced but *Spironucleus* spp. was not eliminated from infected animals. Subsequently, the entire class of 5-hydroxyimidazole compounds has been removed from the US market because of potential carcinogenicity concerns.

Prevention

Prevention is based on good colony management, which includes proper sanitation of caging and isolation, testing, and quarantine procedures. Cysts are resistant to commonly used disinfectants. Cysts of *S. muris* are sensitive to temperatures above 45 °C (113 °F) for 30 minutes or 60 °C (140 °F) for 1 minute, 70% ethanol, and 4% formalin. They survive cold, low pH, and desiccation. Cesarean derivation and cross-fostering onto clean dams can be used to rederive infected animals.

Public Health Significance

S. muris is not pathogenic for humans.

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STAPHYLOCOCCOSIS

Hosts

S. aureus infections occur commonly in a variety of animals, including humans. The organism is an opportunistic agent and is commonly carried subclinically in the nasopharynx and on the skin of rabbits and rodents. Staphylococcal abscesses are common in some colonies of immunocompromised mice, and staphylococcal dermatitis occurs from time to time in rats and other rodent species, possibly secondary to undetermined genetic, autoimmune, and other inciting causes.

Etiology

S. aureus is an aerobic, nonsporeforming, variably alpha- and beta-hemolytic, catalase-positive, Gram-positive coccus. Although several human phage types have been recovered from animals, animals usually have species-specific staphylococcal serotypes or biotypes.

Transmission

Two important considerations in the transmission and persistence of *S. aureus* are human carriers and the resistance of the organism to drying and environmental factors. The organism may spread by direct contact between animals and man or by contaminated food, feces, cages, and bedding. Aerosol spread is possible also, as is invasion through traumatized skin or open umbilical stumps.

Predisposing Factors

Staphylococci are common microflora of the skin, mucous membranes, and upper respiratory tract. Initiation of clinical disease usually involves a cutaneous wound, constant skin wetting, or a stressor, such as crowding, dietary changes, fighting, low dietary protein, or high environmental temperatures. Contact with infected caretakers has been implicated as a predisposing factor.

Clinical Signs

Clinical signs of *S. aureus* infection, other than sudden death from pneumonia, septicemia, or toxemia, include fever, anorexia, depression, urinary tract infections, moist dermatitis, conjunctivitis, foot swelling, subcutaneous lumps, enlarged mammary glands, or a purulent discharge. Pruritic skin lesions may elicit self-mutilation or the animals may develop scabs and heal spontaneously. Dermatitis is often exacerbated by scratching. Infections caused by infectious agents such as *Staphylococcus* spp. may alter sleep patterns.

Among the staphylococcal dermatopathies, which range from alopecia and reddening to extensive ulceration, are cheilitis and exfoliative dermatitis in guinea pigs; ulcerative to gangrenous pododermatitis of rabbits, chinchillas, guinea pigs, and rats; pustular and ulcerative dermatitis in rats and mice; ulcerative dermatitis and "sore nose" in gerbils; conjunctivitis in rabbits; mastitis and subcutaneous abscesses in chinchillas and rabbits; and moist dermatitis due to ear tag irritation in mice.

Internal staphylococcal lesions, which may have specific (purulent discharge) or nonspecific signs, include acute-to-chronic rhinitis, gingivitis, pneumonia, and cystitis. Abscessation or suppuration can occur in any tissue, including the tympanic bullae, preputial glands, brain, heart, urogenital system, lymph nodes, and spleen. Death following *S. aureus* infection may be peracute, likely related to exotoxin elaboration. Staphylococcal mastitis in rabbits, originating from

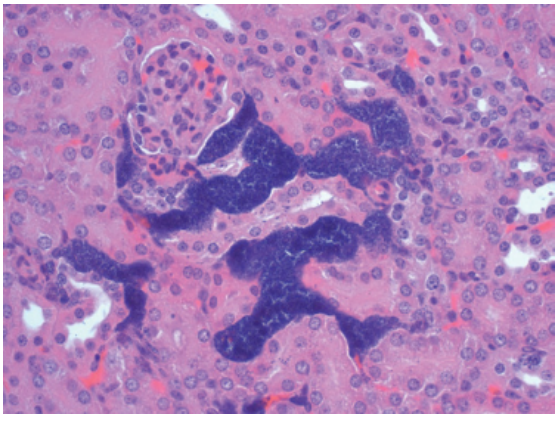


FIGURE 5.30. Section of a kidney from a mouse with staphylococcal septicemia. Multifocal bacterial aggregates are seen.

scratches, bites, or nest box wounds, results in a variation of the "young doe syndrome." The resulting toxemia involves swollen glands, fever, anorexia, and death in nursing does. The young may also die.

Necropsy Signs

Lesions of staphylococcal infection vary with host, site, and duration, but characteristics range from diffuse cellulitis to suppuration with abscessation, necrosis, and granuloma formation. Clumps of large Gram-positive cocci (Figure 5.30) are readily seen on impression smears or in lesions examined microscopically.

Diagnosis

Recovery of *S. aureus* on culture does not confirm a diagnosis, although it does confirm the presence of the organism at the site. Other bacteria, including *Pasteurella* spp., *Salmonella* spp., *Pseudomonas* spp., and *Streptococcus* spp., produce dermatitis or abscessation in rabbits and rodents. Trimming toenails may be useful to reduce self-mutilation.

Treatment

Treatment of staphylococcal infections, if indicated, includes cleaning, drainage, or excision of the lesion; removal of the cause of traumatic insult, if any; and selection of topical and parenteral antibiotics based on culture, sensitivity testing, and host idiosyncrasies.

Rodents are active groomers and quickly remove and consume materials applied topically. Topical agents, such as zinc ointment, should be applied in a thin coat, and often over-the-counter medications can provide soothing relief without upsetting gastrointestinal flora. Elizabethan collars, properly constructed and applied, may be useful in preventing animals from removing topical preparations.

Antibiotics that have been used to treat staphylococcal infections include gentamicin, kanamycin, procaine penicillin G (20,000–40,000 units/kg for three days), nitrofuran topical ointments, oxytetracycline (55 mg/kg fresh daily in water for four days), and tetracycline hydrochloride (0.3 g/100 mL water for 14 days). Penicillins and cephalosporins are generally well tolerated in mice and rats but may induce fatal dysbiosis when used in rabbits and other rodent species.

Prevention

The spread of *S. aureus* or the initiation of clinical disease in carrier animals is reduced or prevented by good sanitation, elimination of sharp or abrasive surfaces, use of clean feed and bedding, reduction of stress, and monitoring of caretakers and animals. Elimination of carriers by treatment is difficult.

Public Health Significance

Strains of methicillin-resistant *S. aureus* (MRSA) have been cultured from clinically normal rabbits, guinea pigs, and chinchillas. Appropriate hand-washing practices should always be used after handling small rodents and rabbits.

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STREPTOCOCCUS PNEUMONIAE INFECTIONS IN RODENTS

Hosts

S. pneumoniae affects a wide range of animals, but the guinea pig and rat are particularly susceptible. Rabbits, mice, and other small rodent species are less susceptible.

Etiology

S. pneumoniae infections in the guinea pig are caused by serotypes III, IV, and XIX. Serotypes reported in rats include II, III, VIII, XVI, and XIX. *S. pneumoniae* are Gram-positive, oval or lanciform, capsulated cocci that often occur in distinct pairs or short chains. Genus synonyms are *Diplococcus* spp. and *Pneumococcus* spp. Infections in rodent colonies tend to be monotypic.

Transmission

Transmission of *S. pneumoniae* is by respiratory aerosol or direct contact. Clinically normal guinea pigs and rats may carry the organism in the upper respiratory passages. Depending on the season of the year, 40–70% of human populations carry *S. pneumoniae* in the respiratory passages and may be the source of the infection in animals.

Predisposing Factors

Losses from *S. pneumoniae* are greater during the winter, after shipment, and in animals on marginal diets, especially in guinea pigs with hypovitaminosis C. Carrier animals frequently succumb when stressed by dietary deficiencies, concurrent diseases such as mycoplasmosis and Sendai virus infection in rats, pregnancy in guinea pigs, experimental procedures, shipment, and poor husbandry. Inbred strains of guinea pigs are more susceptible than are random or outbred stocks. Infected animals should not be used in research.

Clinical Signs

Carrier animals may have upper respiratory infections without clinical signs. Acute episodes or prolonged epizootics with variable morbidity and mortality may both occur. In guinea pigs, clinical signs include sneezing, nasal and ocular discharges, anorexia, weight loss, coughing, dyspnea, depression, and torticollis if the inner ear or brain is affected, and death. Abortions are associated with both general and uterine infections.

Similar signs, along with hematuria, are seen in affected rats. Carrier rats and guinea pigs, after experimental manipulations, are prone to clinical disease due to *S. pneumoniae*, for example, peritonitis after intraperitoneal injections, encephalitis after placement of intracranial implants, and pleuritis after cardiac puncture.

Necropsy Signs

Gross lesions of *S. pneumoniae* infection include seropurulent and fibrinopurulent polyserositis, including pleuritis, pericarditis, epicarditis, peritonitis, orchitis, meningitis, otitis media and interna, metritis, and bronchopneumonia.

Diagnosis

Diagnosis is established by observation of the Gram-positive, oval or lanciform, coccal bacteria in pairs or short chains on a stained, direct smear of the inflammatory exudate. Cultures for routine monitoring can be collected from the nasal passages with a small swab or by nasal lavage. Histologically, unlike with many bacterial diseases, large numbers of organisms can be seen in smears and tissue sections. Recovery of *S. pneumoniae* on blood agar culture in the presence of 5–10% CO_2 confirms the diagnosis. An ELISA is available for serodiagnosis of pneumococcal infections.

Treatment

Treatment in most cases is impractical because the condition may be advanced at the time of detection. Antibiotic therapy likely will not eliminate the agent from infected colonies. Oxytetracycline at 0.1 mg/mL in the drinking water for seven days has controlled an epizootic but not eliminated the carrier state. Such treatment assumes that the animal will drink the liquid and tolerate changes in intestinal flora, and that the antibiotic will reach the organisms. *S. pneumoniae* organisms are generally sensitive to benzathine-based penicillins, ampicillin, bacitracin, chloramphenicol, erythromycin, lincomycin, and methicillin, but most of these antibiotics may produce fatal reactions in guinea pigs. Broad-spectrum antibiotics such as chloramphenicol and trimethoprim–sulfa may be useful in guinea pigs. For rats, 150 units/g body weight of benzathine penicillin has been recommended.

Prevention

Good husbandry, closed-colony maintenance, elimination of carriers, and reduction of environmental stress reduce the possibility and severity of outbreaks. Ordinary disinfectants readily kill pneumococci. A vaccine that contains capsular polysaccharides from multiple serotypes is used to prevent human infections. To minimize shedding and bacterial transmission, human caregivers with streptococcal infections should not handle rabbits or rodents.

Public Health Significance

S. pneumoniae can cause respiratory and meningeal disease in humans, especially in elderly people, and in people who lack spleens. In some cases, the serotypes that affect animals may also affect humans.

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STREPTOCOCCUS ZOOEPIDEMICUS INFECTIONS IN GUINEA PIGS

Hosts

Streptococcal organisms are found in a variety of hosts, but among small rodents the guinea pig is most often affected clinically with *S. zooepidemicus*.

Etiology

A beta-hemolytic, Gram-positive, encapsulated, Lancefield's Group C *Streptococcus*, *S. zooepidemicus* is involved occasionally in clinical disease in conventionally housed pet and laboratory origin guinea pigs. The cervical lymphadenitis caused by this agent closely resembles a less common disease caused by *Streptobacillus moniliformis*.

Transmission

Transmission of *S. zooepidemicus* occurs through cutaneous wounds, via aerosol into the respiratory tract, or by the genital route. In many cases, the agent likely enters the host through small abrasions in the oral cavity. The oral cavity abrasions may be caused by sharp or coarse plant feeds, such as hay and oats. After penetration, the agent is transported via the lymphatics to the draining regional cervical lymph nodes, where it proliferates. The conjunctiva and nasal mucosa represent excellent sites for entry of *S. zooepidemicus* infections that result in cervical lymphadenitis in young guinea pigs.

Predisposing Factors

Poor husbandry and general stress factors predispose to streptococcal infections. Biting facilitates transmission, as does the traumatic effect of overgrown teeth and coarse dietary roughage. Dietary deficiencies, especially vitamin C deficiency in guinea pigs, must be resolved, as they may predispose the animals to infection.

Clinical Signs

In its chronic or enzootic form, *S. zooepidemicus* causes cervical lymphadenitis, a sporadic, pyogenic infection with abscessation and, in many cases, external drainage of the ventral cervical lymph nodes. Abscesses caused by this agent may occur in almost any organ, but cervical and other lymph nodes are by far the most common site. This lymphadenopathy is sometimes referred to as "lumps." Septicemias and acute pneumonias with high mortality occur in the epizootic form.

Torticollis or "wry neck" results from streptococcal infection of the middle ear with variable extension to the inner ear. Respiratory involvement is manifested clinically by nasal and ocular discharge and by signs of acute pneumonia, including dyspnea and cyanosis. Chronic infection can progress to septicemia if the host is stressed or an abscess ruptures spontaneously or is opened surgically. Abortions, stillbirths, hematuria, and hemoglobinuria have been associated with septicemias. Reproductive patterns also may be disturbed by the numerous small uterine abscesses seen in some *S. zooepidemicus* infections.

Necropsy Signs

Infection with *S. zooepidemicus* ranges from an acute, fatal septicemia to a chronic, suppurative process in the lymph nodes, especially the cervical nodes, thoracic and abdominal viscera, uterus, and middle and inner ears. Extensive pulmonary consolidation, focal hepatic necrosis, and fibrinous pleuritis are additional signs.

Diagnosis

A presumptive diagnosis can be made when cervical abscesses are palpated or observed. Chains of Gram-positive cocci may be seen in stained direct smears of material from abscesses. Confirmatory diagnosis depends on *in vitro* culture from abscesses, heart blood, or affected lungs in the case of acute disease. At 24 hours on blood agar, beta-hemolytic colonies of streptococci are mucoid, 2–3 mm in diameter, and are surrounded by a clear zone of hemolysis.

Treatment

Concerns in therapy include the number of infected and contact animals, distribution of abscesses, presence of fistulous tracts, potential for septicemia if the abscess is opened, and the antibiotic sensitivity of the organism. Abscesses should be removed intact from anesthetized animals, whenever possible, to minimize environmental contamination and transmission to other guinea pigs in the household or colony. With or without surgical treatment, a systemic antibiotic, such as chloramphenicol, enrofloxacin or ciprofloxacin (10 mg/kg IM or PO every 12 hr), or trimethoprim–sulfa is given. Chloramphenicol palmitate, one of the few antibiotics safe to use in guinea pigs, is given at 50 mg/kg orally for 5–7 days.

Prevention

Epizootics with high mortality usually follow introduction of affected stock into a formerly infection-free colony or mixing susceptible stock with resistant carrier animals. Good husbandry

practices, general preventive measures, and routine palpation for enlarged cervical lymph nodes reduce the possibility of streptococcal infection in guinea pigs. Affected guinea pigs are removed from the colony or treated until the abscesses have drained and healed. In cases of epizootic *S. zooepidemicus* infection with widespread pneumonia, septicemias, and abscesses, the entire colony may have to be eliminated.

Killed bacterins have not been effective in preventing this disease, but scratch injections into the oral cavity with American Type Culture Collection strain 12960 of a group C *Streptococcus* has stimulated immunity. The organism is grown for 24 hours in trypticase soy broth and 0.1 mL is scratched into the oral mucosa.

Public Health Significance

Beta-hemolytic streptococci (not *S. zooepidemicus*) are recovered frequently from human infections, but *S. zooepidemicus* is strictly an animal pathogen.

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TRANSMISSIBLE COLONIC HYPERPLASIA IN MICE

Hosts

Transmissible murine colonic hyperplasia caused by *Citrobacter rodentium* is a naturally occurring disease seen predominantly in mice; however, infections have also been reported in guinea pigs and gerbils.

Etiology

The causative agent of transmissible colonic hyperplasia is a Gram-negative bacillus, formerly designated as *Citrobacter freundii* 4280 and more recently as *C. rodentium*. Transmissible murine colonic hyperplasia is a naturally occurring infectious disease of mice characterized by mucosal hyperplasia of the distal colon. *C. rodentium* is related to *E. coli* strains and induces attaching and effacing lesions. Following oral inoculation, the organism initially colonizes the small intestine and then selectively colonizes the descending colon, attaching to the mucosa and displacing other aerobic bacteria and inducing an intense mucosal hyperplasia.

There are isolated reports of *C. rodentium*–associated enteric disease in gerbils and guinea pigs.

Transmission

Transmission of the causative bacterium is by the fecal–oral route. Fomites may be involved in cage-to-cage spread. Outbreaks in a colony are often prolonged over weeks or months, although the duration of infection in any individual animal is likely short. The source of infection for mouse colonies frequently remains unknown. Humans are suspected carriers.

Predisposing Factors

Dietary changes, diet composition, age, genetic background, stress, and virulence of the *C. rodentium* strain affect susceptibility to clinical disease. Newly weaned mice have a higher mortality and more obvious clinical signs than do older mice. C3H mice have more severe clinical signs than do NIH Swiss, C57BL/6, and DBA/2 mice.

Clinical Signs

Clinical signs include ruffled hair coat, stunting, passage of dark, sticky feces, and occasionally rectal prolapse. Moderate mortality occurs in mice infected at around 2–6 weeks of age, and mortality rates are low to nil in mice infected as adults. There is a great variation in strain susceptibility to the clinical disease, and diet may also influence susceptibility. After the acute phase, colonic hyperplasia regresses.

Necropsy Signs

The outstanding sign at necropsy of affected mice is a grossly detectable thickening (to 0.5 cm diameter) and turgidity of the rectum and terminal 1–3 cm of the descending colon. The thickening is due to hyperplasia of enterocytes, a reaction in both young and adult mice. Inflammation accompanies the hyperplasia in young mice.

Microscopically, mucosal hyperplasia is seen in the descending colon. There is a marked increase in the height of the affected mucosa (crypt height may be up to three times normal), increased mitotic index, erosions of affected epithelium, presence of bacterial colonies in crypts and lamina propria, leukocytic infiltration, and goblet cell hyperplasia.

In gerbils, the clinical signs and pathology are similar to those seen in laboratory mice.

Diagnosis

Diagnosis is based on recovery of *C. rodentium* from affected mice and on the characteristic colonic hyperplasia. *C. rodentium* is normally recoverable on culture only during the early

stages of the disease. When present, the agent is readily cultured *in vitro* and has a characteristic biochemical reaction profile. Most isolates are lactose positive and use citrate as a sole source of carbon.

Nonpathogenic *Citrobacter* biotypes are commonly isolated from the intestines and feces of rodents; thus, microbiologists working with rodent samples must be aware of *in vitro* tests necessary to distinguish the pathogenic *C. rodentium* biotypes from other nonpathogenic biotypes. Other enteric diseases of mice that should be considered in the differential diagnosis include enzootic diarrhea of infant mice, MHV infection, giardiasis, reovirus and rotavirus infections, colibacillosis, salmonellosis, spironucleosis, *Helicobacter* spp. infection, pinworm infestation, and *Clostridium piliforme* infection (Tyzzer's disease).

Transmission to sentinel animals via dirty bedding transfer is inefficient, and this method may not detect the presence of the bacterium.

Treatment

Ingestion of 0.1% solution of sodium sulfamethazine in the drinking water for 60 days has reduced clinical signs of experimental *Citrobacter* spp. infection in a mouse colony. Enrofloxacin treatment is reported to suppress the disease and eliminate the bacteria in mice. Ideally, animals should be rederived by cesarean section or embryo transfer to produce a clean, disease-free colony.

Prevention

Good husbandry and sanitation will reduce opportunities for entry of the bacterium into a colony. *C. rodentium* is occasionally isolated from the intestinal tracts of clinically normal mammals, including laboratory rodents and man, a finding that raises concerns about sources of contamination.

Public Health Significance

C. rodentium variants have been found in human feces, but the potential pathogenicity of these and other *Citrobacter* spp. for humans is unknown. *C. rodentium*–infected mice are commonly used as a model for enteropathogenic E. coi infections of humans.

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TULAREMIA

Hosts

Tularemia is a common, often fatal septicemic disease of over a hundred species of wild animals, especially rodents, wild lagomorphs, and certain gallinaceous birds (pheasants and quail). Tularemia has a broad host spectrum, and rodents and lagomorphs are highly susceptible and have been involved in many epizootics. Tularemia is rare in domestic rabbits and rodents, although animals raised outdoors and exposed to ticks are much more likely to contract infections than are similar animals kept indoors in a home or laboratory animal resource facility.

Etiology

Francisella tularensis is an aerobic nonmotile, Gram-negative, pleomorphic, bipolar coccobacillus. The agent is particularly prevalent in the south central United States and has been classified by US Centers for Disease Control and Prevention as a "select agent," requiring strict containment and documentation for experimental studies.

Transmission

Transmission is direct, via bites, inhalation, or ingestion of bacilli, and has not been documented to occur from human to human. Only a few (5–10) organisms are required for infection by the respiratory route, while many times more are required if ingested (10^6–10^8). Blood-sucking arthropods, especially ticks, biting flies, and mosquitoes, are an important means of bacterial transmission. The tissues, blood, and feces of infected animals harbor the organism.

Predisposing Factors

The tularemia bacterium is highly infectious and affects otherwise healthy animals. The disease is more common in the fall and winter when carrier animals concentrate in buildings and other enclosed spaces to obtain protection from the cold.

Clinical Signs

The disease has a range of signs in mammals depending upon bacterial type, dose, and route of exposure. Symptoms include fever, lethargy, lymphadenopathy, pneumonic disease, septicemia, and death. Affected animals may initially demonstrate a roughened hair coat, depression, tendency to huddle, anorexia, ataxia, and death. The course of the disease in cottontail rabbits (*Sylvilagus* spp.) lasts approximately 1 week. Asymptomatic infections are common in wildlife based on the high prevalence of serum antibody.

Necropsy Signs

Signs of septicemia include pulmonary congestion and consolidation, subpleural petechial hemorrhage, numerous pinpoint, small, and bright white hepatic foci, and congestion and enlargement of the liver and spleen. The miliary white spots on the dark background of the congested liver and spleen have been described as resembling the Milky Way galaxy. Lymph nodes are enlarged and the bacteria are distributed widely in blood vessels.

Diagnosis

Diagnosis is based on necropsy findings of a septicemic bacterial disease. Stained impression smears of affected tissues or fluids may contain small Gram-negative coccobacilli among debris and within cells and can aid in making a tentative diagnosis at necropsy.

In vitro recovery of *F. tularensis* requires special attention. Special enriched media such as blood–glucose–cysteine agar grow colonies that are minute and translucent. The agent is highly hazardous to man and must be handled with extreme caution in the laboratory. Intraperitoneal injection of potentially contaminated blood into a guinea pig produces lymphoid necrosis, serofibrinous peritonitis, septicemia, and death in 8–10 days.

Treatment

Treatment is not indicated for animals. Tetracyclines and streptomycin are among the antibiotics used to treat human infections.

Prevention

Avoid or minimize contact with animals that may have been exposed to *F. tularensis.* Exclusion of wild mammals and insect vectors from the colony is a preventive measure. Hunters should avoid "lazy" cottontail rabbits and wear gloves when skinning game.

Public Health Significance

Up to 90% of human cases of tularemia are linked to wild lagomorph exposure. Humans are very susceptible and tularemia is a reportable disease in the United States. Because contamination of inapparent skin lesions results in human infections, persons handling suspect tissues should always wear gloves. Laboratory culture should be attempted only where adequate biohazard culture facilities are available. Cutaneous lesions, septicemias, and meningitis occur in cases of human tularemia. Bites of two and three host ticks are particularly dangerous, as ticks transmit the bacterium.

Recent cases in humans in Canada and the United States have been associated with pet hamster bites, the hamsters often dying of mysterious illnesses before a diagnosis is determined. In all cases, the infected animals have been traced back to large rodent breeders or distribution centers. Human cases have also occurred after well-meaning individuals have picked up and attempted to treat feral squirrels and rabbits that appeared sick. If these animals are taken into clinics for evaluation, it is important to ensure that appropriate hygiene and personal safety measures are in place to minimize the risk of potential disease transmission.

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TYZZER'S DISEASE (*CLOSTRIDIUM PILIFORME* INFECTION)

Hosts

The number of species known to be susceptible to Tyzzer's disease, an infection caused by *C. piliforme*, continues to increase. The spectrum includes mice, rats, hamsters, gerbils, rabbits, guinea pigs, chinchillas, horses, cattle, rhesus monkeys, marmosets, cats, dogs, several wildlife species, and others. Tyzzer's disease is a common disease of gerbils and is found occasionally in rats, rabbits, and other rodents. Many

research rat and rabbit colonies have a high incidence of seropositive animals without evidence of clinical disease. Rat, hamster, and mouse colonies (barrier- and nonbarrier-sustained) may have clinically inapparent infections.

Etiology

C. piliforme is a spore-forming, motile, narrow, rod-shaped, PAS-positive, nonacid-fast, obligate, Gram-negative intracellular organism. Each species of animal seems to have a specific substrain of *C. piliforme*, but within some animal species there may be multiple substrains of the bacterium. The organism is a common benign intestinal inhabitant that persists for years in spore form outside the host. *C. piliforme* has been grown in tissue culture, and it can be propagated in embryonated hen eggs.

Transmission

Transmission occurs by the fecal–oral route. Infectious spores survive for a year or more in bedding, soil, or contaminated feed. The vegetative form is extremely labile.

Predisposing Factors

Poor environmental sanitation, shipping stress, and immunosuppressive therapy such as radiation, corticosteroids, concurrent disease, thymectomy, and crowding contribute to the development of clinical disease. The acute, highly fatal disease is seen most often in weanling animals, but adults also may be affected. Use of sulfaquinoxaline to prevent coccidiosis and pneumonia in rabbits has been associated with an epidemic of Tyzzer's disease.

Clinical Signs

The most common form of infection is subclinical and immunocompetent animals can clear the infection efficiently. Tyzzer's disease in weanling or stressed animals is a peracute-to-acute enzootic disease causing rough hair coat, lethargy, and death within 48–72 hours. Watery diarrhea and perineal fecal staining may or may not accompany the disease. Chronically infected animals, in which hepatic lesions may be more pronounced, exhibit weight loss, rough hair coat, and eventually death.

Necropsy Signs

The classical lesions of *C. piliforme* infection consist of a triad typically involving the gut, liver, and heart. The liver may be enlarged with few to numerous necrotic foci, 1–2 mm in diameter. The liver is not necessarily involved, and the intestine or heart may be the only organs affected. The absence of liver lesions does not rule out Tyzzer's disease. In more acute cases, there may be edema, congestion, hemorrhage, and focal ulceration of the intestine, particularly around the ileocecal–colonic junction. The gut is often atonic and filled with a yellowish fluid. Mesenteric lymph nodes may be enlarged. The abdomen and small intestine of affected rats may be distended grossly due to megaloileitis. Five-week-old SD rats from seropositive colonies had a low incidence of megaloileitis, while seronegative colonies had no megaloileitis. A proteinaceous exudate may be found in the abdominal cavity of infected guinea pigs and gerbils. Pale myocardial foci have been noted in rabbits, rats, mice, and hamsters with Tyzzer's disease. There are no reports of splenic lesions.

The hepatic, intestinal, and myocardial foci that variably characterize this disease represent areas of necrosis surrounded initially by a scant, mixed inflammatory cell population. These foci probably arise via an embolic shower of organisms from a primary infection in the intestine. The filamentous organisms may be seen in tissue sections within the cytoplasm of cells adjacent to the necrotic area using a Steiner or Warthin–Starry silver stain, often in a "bundle of sticks" arrangement.

Diagnosis

Necropsy signs and tissue sections stained with silver, Giemsa, or PAS stains demonstrate the intracellular, filamentous *C. piliforme* organisms in hepatocytes, enterocytes, or other tissues, providing a definitive diagnosis of Tyzzer's disease. Indirect fluorescent antibody tests are also a diagnostic aid. PCR assays may be helpful to determine if animals are shedding the bacterium in their feces.

The diagnosis of Tyzzer's disease may be difficult to establish. Even with special stains, organisms in tissues may be difficult to find because of their paucity. Feces from suspect animals inoculated per os into known *C. piliforme*–free weanling gerbils (which are highly susceptible) is a valuable aid for detecting the presence of the Tyzzer's disease agent in a suspect colony. Little is known about the incidence of Tyzzer's disease among animals in commercial and private stock colonies because colonies are not screened regularly for Tyzzer's disease, in part because of the absence of a good screening test.

Treatment

The peracute-to-acute (one- to four-day) course of the disease and the intracellular location of the organism reduce the effectiveness of treatment. Oxytetracycline in the drinking water at 0.1 g/L for 30 days has suppressed an outbreak. Tetracycline at 10 mg/kg body weight for 5 days "on–off–on" or at 400 mg/L for 10 days has also been used. The agent of Tyzzer's disease is also sensitive to penicillin, cephalosporins, and erythromycin.

Prevention

Purchase of stock from a reputable vendor, preferably one using cesarean derivations and barrier-rearing techniques, and good husbandry practices are the best preventive measures. Antibiotics may suppress infections, but carriers may develop.

Spores survive freeze–thaw cycles but are killed if heated at 56 °C (133 °F) for 1 hour or 80 °C (176 °F) for 30 minutes. Spores are resistant to ethanol and quaternary ammonia compounds and may persist in the environment. A 0.5% sodium hypochlorite solution and peracetic acid are effective in spore inactivation. Filter cage covers (i.e., microisolator cages) aid in reducing transmission. Traditional rederivation methods have successfully eliminated Tyzzer's disease from a large rat-breeding colony.

Public Health Significance

No public health significance is known, but the report of *C. piliforme* infection in a rhesus monkey and an immunosuppressed human should be noted. Antibodies to *C. piliforme* have been found in pregnant women. Because *C. piliforme* affects such a wide spectrum of animal species, humans are likely susceptible to clinical disease under certain circumstances, such as systemic immune deficiency.

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ULCERATIVE DERMATITIS (MOIST DERMATITIS)

Hosts

Ulcerative or moist dermatitis occurs sporadically in rabbits and rodents.

Etiology

Ulcerative dermatitis or moist eczema refers to a localized reddened exudative inflammatory skin lesion that can be caused by a variety of mechanical lesions or irritating infectious agents. Generally, bacterial agents cannot become established unless the skin is traumatized or continually wetted. Noninfectious factors include scratching at an allergic reaction site, abrasions, cuts, puncture wounds, urine scald, fight wounds, and chemical or thermal burns. Bacteria involved may include *Staphylococcus* spp., *Treponema* spp., *Streptococcus* spp., *Fusobacterium* spp., *Corynebacterium* spp., and *Pseudomonas* spp., whose blue-green pigment causes "blue fur" disease. Specific or named conditions include "sore nose" in gerbils (discussed earlier in the chapter) and "wet dewlap," "slobbers," ptyalism, and "hutch bum" in rabbits.

In mice, the condition is considered multifactorial, and defining a specific etiologic cause has been elusive despite years of research by many laboratories. The syndrome has been variously associated with immune-mediated vasculitis, innate immune dysfunctions, and behavioral peculiarities of C57BL/6 and related strains. The condition may be associated with a non-H2 linked gene or combination of genes but has an epigenetic component, and the syndrome is exacerbated by the presence of mites or ectoparasites. A retrospective study found that 4.1% of C57BL/6 mice became affected with the condition during their lifetime, and it was more common in female mice that were 10–16 months of age.

Predisposing Factors

Conjunctivitis, drooling from malocclusion or other dental disease, use of water pans and crocks, leaking sipper tubes, chronic diarrhea, obesity, urinary incontinence, parasitisim, and damp cages predispose to moist dermatitis. Overcrowding, stress, fighting, and the use of abrasive or nonabsorbent bedding or in-cage resources may exacerbate or aggravate moist dermatitis conditions. Reducing or eliminating these factors may result in alleviation of signs.

Clinical Signs

Ulcerative dermatopathies may range from superficial erythema with minimal exudation to suppuration and deep ulceration. Regional lymph nodes may be enlarged if the dermal reaction is extensive. The hair surrounding the lesion is usually moist and matted. Lesions occur most frequently on the face or ventral areas in contact with water. Frequently, *Staphylococcus* spp. can be recovered from the inflamed or ulcerated areas. Pyocyanin, a pigment produced by some strains of *Pseudomonas aeruginosa*, sometimes imparts a blue-green color to affected fur. *P. aeruginosa* also produces several toxins that cause dermal necrosis and may be lethal.

Ulcerative dermatitis of rats is seen more often in young males. The lesions, which usually begin on the neck, shoulders,



FIGURE 5.31. Severe ulcerative dermatitis in a C57BL/6 mouse.

or anterior trunk, first appear as an irregularity in the hair coat. This small focus of alopecia or ulceration then enlarges over the next several days to form small-to-extensive ulcerations. Some lesions scab and regress, and others are pruritic and stimulate scratching and self-mutilation, necessitating euthanasia.

Ulcerative dermatitis is a common disease of mice of C57BL/6 background. The condition presents with pruritus and can result in alopecia, ulceration, crusting, exudation with potential secondary bacterial infections, and skin necrosis (Figure 5.31). The lesions are most often observed on the back of the head, neck, and between the scapula but can extend into the axilla, ventrum, and inguinal areas.

Diagnosis

Diagnosis is aided by microbiologic culture and microscopic examinations of lesions.

Treatment

Ulcerative dermatitis is treated by clipping hair over and adjacent to the lesion, cleansing the area affected, administering topical or systemic antibiotics or applying an antiseptic, and removing the underlying cause. Toe nails should also be checked and trimmed with clippers if overgrown.

In mice, treatment can be frustrating and animals must often be euthanized because of extensive ulceration of the skin. One study evaluated the consequences of treating the condition by dietary vitamin E supplementation (0.1 mL Derm Caps® PO once daily for 7–10 days) at the onset of clinical signs. Of 71 mice, 45% had complete reepithelialization of the skin with an average recovery time of 2–5 weeks following institution of therapy.

Other therapies attempted in mice and rats include topical triple antibiotic ointment applied once every other day, topical cyclosporine therapy (0.2% cyclosporine in 2% lidocaine supplemented with 50 µg/mL gentamicin) once or twice daily until resolved, and zinc oxide ointment applied topically every 1–2 days.

Prevention

Prevention includes using nonabrasive bedding that is maintained clean and dry in a nonabrasive, dry cage. Use of hopper feeders and sipper tube waterers instead of bowls and crocks reduces throat abrasion and wetting. Balls or stones placed in water crocks reduce wetting while drinking. Obesity is often associated with this syndrome, so proper nutrition and activity reduce risk of occurrence. The water supply is a frequent source of *P. aeruginosa* infections and the sanitation schedule for watering implements, and the source should be checked for this bacterium if a clinical problem develops. Ensuring physical separation opportunities are present as well as multiple forms of nesting material may help to reduce fighting and aggression.

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UROLITHIASIS

Hosts

Uroliths (stones in the urinary tract) occur most commonly in rabbits, rats, and guinea pigs. The predominant mineral in urinary concretions of rabbits and guinea pigs is calcium (calcium carbonate, calcium phosphate, and calcium oxalate) with much smaller amounts of magnesium and phosphorus (ammonium magnesium phosphate or struvite). In rats, struvite uroliths predominate.

Etiology and Predisposing Factors

Although the cause of urolith formation is obscure, predisposing factors include genetic predisposition, metabolic disorders, nutritional imbalances, inadequate water intake,

nematode infestation (*Trichosomoides crassicauda* in rats), and bacterial infections. Typically, signs of urolithiasis are more common in males because their urethra is longer, narrower, and less distensible than in females, resulting in partial or complete urethral obstruction when stones are present.

The predisposition of rabbits to develop calcium-containing renal and urinary calculi may be related to peculiarities in the calcium metabolism of this species. Excessive calcium intake is regulated through greatly increased elimination by the kidneys, not by reduced absorption in the intestine, which increases the risk of precipitation of urinary solutes, especially if the urine pH becomes too alkaline. Normal rabbit urine pH is 8.2. At pH 8.5–9.5, crystals precipitate in the urine. Guinea pigs have a similar calcium physiology to some extent.

In a colony of 170 guinea pigs, aged females were more predisposed to cystitis and urolithiasis than were males and young guinea pigs. The cause may have been related to infection of the urinary tract with *E. coli* or *Staphylococcus* spp., irritation and trauma of the urinary bladder due to the cystic calculi, preexisting diabetes mellitus, and female guinea pig urogenital anatomy and function (shorter urethra and ease of bacterial retrograde movement). In another study, *Corynebacterium* spp. was a frequent isolate in conjunction with bladder urolithiasis.

In an outbreak of pneumonia and septicemia due to *Streptococcus pyogenes* in a breeding colony of 800 guinea pigs, 50% of the adult females had urolithiasis, which was believed to be a sequela of cystitis caused by the streptococcal infection.

Clinical Signs

Signs of urolithiasis in rabbits may be absent or may include anorexia, weight loss, listlessness, hunched posture, anuria or hematuria, and dense abdominal masses evident by palpation or on radiographs. Discrete urinary stones may be difficult to distinguish from calcium "sludge" that is common in rabbit urinary bladders. Affected rabbits may have an abnormal serum biochemical profile, although nonrenal factors may affect BUN levels, and serum creatinine levels do not generally increase until 75% or more of renal function is lost. Urine may be difficult to express because of calcium sludging or because of urethral or ureteral obstruction by calculi, in which case the urinary bladder may be quite turgid.

Perineal soiling and urine scald may be seen with pollakiuria and incontinence, further contributing to animal discomfort.

Necropsy Signs

On necropsy, fine sand or numerous irregularly shaped stones, all of about the same size, may be found in the renal pelvis, ureters, bladder, or urethra. Structures between the nephron and the concretion may be dilated and filled with fluid. Cystitis is a common sequela to urinary stasis.

Urethral proteinaceous obstructions occur in aged male guinea pigs, rats, and mice. These are composed primarily of congealed ejaculum that may become infected; a suppurative infection ensues. A variety of bacteria may be isolated from these infections, especially *P. aeruginosa*, *E. coli*, and *Proteus* spp.

Diagnosis

Diagnosis is based on clinical signs, palpation, radiography, abdominal ultrasound, urinalysis, culture, and a chronic hematuria refractory to antibiotic therapy.

Treatment

In general, diets to dissolve uroliths are ineffective in rabbits and rodents. Treatment for urolithiasis is surgical removal of calculi with a guarded prognosis for long-term cure, particularly in the case of renoliths, as recurrence of calculi is common. Postoperative management should include an appropriate course of antibiotics preferably based on urine culture and sensitivity testing (chloramphenicol, trimethoprim–sulfa, and enrofloxacin are all potential selections), a low-calcium diet that limits pellets and alfalfa intake, and follow-up radiographs.

T. crassicauda infection in rats may be treated with ivermectin at 3 mg/kg PO (0.4% w/v solution of ivermectin in propylene glycol) given with a 1 mL syringe and polyethylene tubing.

Prevention

Because of the uncommon occurrence and uncertain etiology of urolithiasis, specific preventive measures, other than good husbandry practices and a balanced diet, have not been described. A standard recommendation for preventing urolithiasis in non-breeding pet rabbits is to reduce the dietary component of high-calcium pellets and to increase the amount of grass hay. Not feeding rabbits more calcium than is required, around 5 g/kg (maintenance) and approximately 8 g/kg (growth, lactation) and less than 25 µg (1000 IU) cholecalciferol/kg diet, has been recommended to control urinary stones, gravel, and calcium sludge.

There may be sufficient empirical justification for combining a grass hay of lower calcium content with a limited pelleted diet if plasma calcium levels exceed 16 mg/dL (4 mmol/L) or if there are signs of metastatic calcification or urolithiasis. Young, old, or lactating rabbits may not obtain sufficient energy from a higher fiber feed. Excessive vitamin D supplementation should be avoided in all species to minimize the risk of urolith development. Increasing water intake may also be helpful.

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VENEREAL SPIROCHETOSIS (TREPONEMATOSIS)

Hosts

Domestic rabbits, wild lagomorphs, and hares are susceptible to venereal spirochetosis. The disease is also known as treponematosis, rabbit syphilis, and vent disease.

Etiology

Treponema paraluiscuniculi is a slender, spiral-shaped bacterium between 10 µm and 30 µm in length. Antibodies to *T. paraluiscuniculi* cross-react with antigens of *T. pallidum*, the agent of human syphilis.

Transmission

The spirochete is transmitted by direct contact, especially during mating. Exchange of bucks among breeders promotes dissemination of the organism. Infection of kits may occur at birth or during the nursing period, but infection is uncommon in virgin rabbits. The disease is uncommon in most well-managed rabbit colonies but may be seen occasionally in pet rabbits and commercial operations.

Predisposing Factors

Rabbits in cold environments are predisposed to the clinical disease. Susceptibility, extent, and severity of lesions vary among rabbit breeds. Breeding animals are at higher risk than individual or laboratory animals.

Clinical Signs

Serologically positive rabbits are often encountered, but clinical, epizootic disease is uncommon. Whereas more attention has been paid to the disease in males because they have more obvious clinical signs, females may also contract the infection. Females may develop metritis, retained placentas, and abortions, possibly unnoticed, which occur at 12–22 days of gestation. The herd may have a history of low conception rates and a high incidence of nest box fatalities in young less than nine days of age. Clinical signs, when they appear, begin with vesicular swelling and reddening followed by dry scaliness of the swollen prepuce and vulva. This early stage is followed by the development of macules, papules, erosions, ulcers, and crusts on the external genitalia, perineal areas, nose (Figure 5.32), eyelids, and lips.

A case has been described of venereal spirochetosis in an adult buck that had a firm, slightly raised, nonpruritic, scab-covered mass on the right nasal margin. The scab was removed easily and revealed a red, ulcerated surface. A modified silver stain was used to visualize spirochetes in the superficial dermis and epidermis.

Affected rabbits remain alert, and the condition regresses after several weeks. If the prepuce is affected severely, apparent and transient infertility may result. Preputial and scrotal scars are indicative of healed lesions.

Necropsy Signs

In most cases, there are no internal gross lesions. The perineal and genital skin and the mucous membranes of the external genitalia are the tissues most often affected, although some cases only involve the external nares. Inguinal lymph nodes may be enlarged. Histologically, the thickened epidermis may be hyperkeratotic, and the dermis infiltrated by monomorphonuclear inflammatory cells, primarily plasma cells.

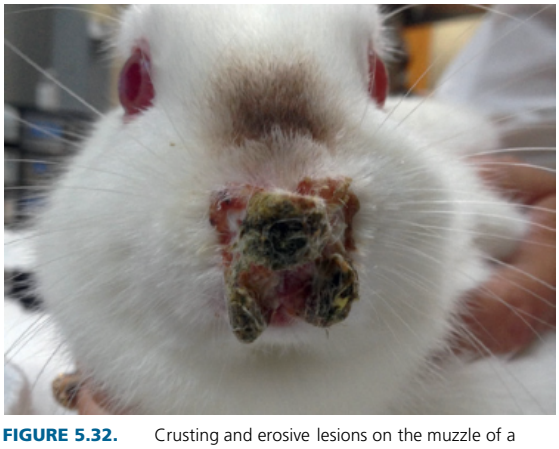


FIGURE 5.32. Crusting and erosive lesions on the muzzle of a rabbit, characteristic of spirochetosis.

Diagnosis

The gross lesions of venereal spirochetosis in rabbits resemble those caused by trauma, dermatophytes, or pasteurellosis (facial crusting). The use of the cardiolipin antigen Wassermann-type test or the rapid plasma reagin (RPR) card test will provide evidence of a *T. paraluiscuniculi* infection. Absence of clinical disease in the absence of concurrent treatment with antibiotics and two negative RPR tests 30 days apart are suggested as evidence of noninfection.

A fluorescent antibody test has also been used in diagnosis. The spirochetes may be demonstrated using darkfield microscopy in wet preparations of tissue fluids expressed from active lesions in the epidermis, dermis, uterus, or lymph nodes. One can also obtain a diagnosis by staining sections of fixed tissue or smears with silver salts. *T. paraluiscuniculi* should be considered in the differential diagnosis of unexpected inflammatory skin lesions in rabbits, especially those around the nose, anus, and genitals.

Treatment

Penicillin given intramuscularly at 40,000 units/kg/day for 3–5 days provides a cure, although penicillin exposure may precipitate an enterotoxemia. Alternately, long-acting penicillin (benzathine penicillin G) can be given intramuscularly at 84,000 units/kg three times at weekly intervals. Owners should carefully monitor animals for signs of enterotoxemia and discontinue antibiotics if animals go off feed or develop diarrhea.

Prevention

Routine serologic screening provides an indication of exposure. Periodic examination of breeding does and bucks for cutaneous lesions followed by treatment or culling will eliminate clinical carriers. Infected animals should not be bred. It may be possible to eliminate the infection from small herds by treating all animals simultaneously. In young animals or fryers bred for meat production, there may be restrictions on the use of certain antimicrobial agents or specific withdrawal times for meat, which must be followed. Maintaining a closed breeding herd prevents introduction of venereal spirochetosis. If new animals must be introduced, they should be clinically and serologically free of disease. It may be advisable to quarantine and treat all new arrivals intended for breeding.

Public Health Significance

Although rhesus monkeys and a chimpanzee have been infected experimentally, humans are not believed to be susceptible to *T. paraluiscuniculi* infection.

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Chapter 6

Case Reports

The case reports described in this chapter were taken, with minor modifications, from the files of diagnostic laboratories at Colorado State University; University of Saskatchewan; University of Guelph; University of California, Davis; Pennsylvania State University; and Mississippi State University. These cases reveal the complexity of disease in rabbits and rodents and demonstrate how field cases may differ considerably from textbook descriptions. Readers may find it helpful to consider how the case would be managed in a private practice versus a laboratory setting. Reference intervals (RI) are provided, where possible, and brief answers and selected references are supplied in the second section of the chapter.



THE RABBIT

Case 1: Acute Abdomen in a Rabbit

A 2-year-old male castrated lionhead rabbit is presented as an emergency for an acute onset of lethargy and anorexia. On physical examination, the rabbit was found to be painful on abdominal palpation and has a larger than normal doughy stomach. The mucous membranes are also pale.

The CBC reveals a low PCV at 25% (RI: 31–50). Serum chemistry indicates an elevation of AST at 470 (RI: 10–140 IU/L), ALT at 487 (RI: 14–80 IU/L), and CK at 6,391 (RI: 150–1,000 UI/L).

a. What is your top differential diagnosis for this clinical presentation?
b. How would you confirm the diagnosis?
c. What treatment would you recommend for this animal?

Case 2: Dyspnea and Bulging Eyes in a Rabbit

A 5-year-old female spayed rabbit was presented for a 2-week history of dyspnea. The owner also described that the eyes appear to be bulging outward. Upon physical examination, you confirm exophthalmos and dyspnea, and you also notice muffled heart sounds.

a. What is your top differential diagnosis for this case?
b. What diagnostic tests would you offer?
c. What treatment options do you recommend?

Case 3: Death in Rabbits Sharing a Lawn with Cats

A distraught laboratory employee consults with you about one of her five prized French lop show rabbits that became sick over the past 2 weeks and died, and a second one that is looking ill. The rabbits are housed in elevated wood and wire mesh hutches in her backyard. The diet consists primarily of commercial rabbit pellets supplemented with fresh vegetables and grass hay. Water is provided ad libitum in bowls. Occasionally, the rabbits are allowed to graze on the lawn. Dogs, cats, raccoons, and foxes are known to wander through the area on occasion.

The rabbit that died had developed varying clinical signs before death, including anorexia, ataxia, muscle tremor, posterior weakness, and paralysis, which lasted approximately 2 days and was followed by death. Examination of the second animal revealed a mild head tilt to the left, weakness on the right, and decreased mentation.

a. What are some differential diagnoses to consider when CNS signs are seen in a rabbit?
b. How would you diagnose an etiologic agent?
c. What is the most likely mode of transmission and source of protozoal or larval migrans disease in the rabbits?
d. What public health concerns do you have?
e. What therapy would you institute and what is the prognosis?

Case 4: Reproductive Disorders in Rabbits

A large commercial rabbitry experienced the following reproductive abnormalities: (1) increased fetal and maternal mortality; (2) kindling rate reduced 25%; (3) increased perinatal and neonatal mortalities; and (4) reduction in average litter size.

Harkness and Wagner's: Biology and Medicine of Rabbits and Rodents, Sixth Edition. Patricia V. Turner, Colette L. Wheler, Hugues Beaufrère, Niora Fabian, and John E. Harkness.
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These problems occurred after feeding a newly formulated diet for 4 months. Postmortem evaluation of does with reproductive disorders (prolonged gestation or abortion) revealed moderate-to-severe suppurative metritis with the recovery of *Pasteurella multocida* from some rabbits. Of the 32 aborted or stillborn fetuses and neonates examined, three aborted fetuses had hydrocephalus and cleft palate. The brains of the affected fetuses had cortical atrophy. All other organs appeared normal. The clinical syndrome involved was suggestive of toxicity or a dietary deficiency manifested by fetal resorption, abortion, stillbirths, and hydrocephalus in the fetuses and neonates.

a. Which vitamins should be implicated as a cause of reproductive abnormalities? Which tissue samples should be submitted for analysis?
b. What are potential causes of a vitamin deficiency or excess? How would you confirm your suspicion?
c. What are other clinical signs of hypervitaminosis A? What are some differential diagnoses of reproductive disorders in the rabbit? What is the potential role of P. multocida in this case?
d. What is the diagnosis?

Case 5: Bloody Urine in a Rabbit

An adult gray chinchilla rabbit doe frequently dribbled several milliliters of bloody urine and reportedly had not eaten for at least 3 days. The student owner brought the rabbit to your clinic for examination.

The perineum was stained with blood, and palpation of the lower abdomen revealed a firm, distended bladder. Radiography revealed an irregularly shaped, opaque mass in the lower abdomen.

a. What is the probable diagnosis? What is the cause?
b. How would you proceed with treatment?
c. What dietary recommendations would you make to the client?

Case 6: Growth Around a Rabbit's Cornea

A 4 month-old pet Florida white rabbit developed a thin fold of tissue surrounding and growing over the upper half of the left cornea. The owner indicated that the growth had been present for approximately 5 weeks, and the rabbit seemed normal otherwise.

The rabbit is sedated and examined and with gentle pressure, the conjunctival fold can be lifted off the eyeball. The abnormal skin is thin and avascular, and there is no evidence of suppurative inflammation.

a. What is the most likely diagnosis?
b. What is the treatment for this condition?
c. What is the prognosis?

Case 7: Ataxia in Dwarf Rabbits

A colony of dwarf rabbits has experienced sporadic deaths among the young. The closed colony is housed indoors in suspended wire cages equipped with crocks for feed and water. In approximately 40% of litters, one kit is affected and at 3–4 weeks of age, these rabbits show clear signs of runting, weakness, and ataxia. The runted animals weighed half that of their normal siblings and invariably die at 10–12 weeks of age. Necropsy has revealed no gross lesions or obvious congenital abnormalities.

a. Which specific conditions in rabbits could produce ataxia?
b. Which common infectious disease of rabbits might produce abnormal neurologic signs?
c. Which tissues should be collected and examined for histologic signs of this disease? Which tissue stains might be used?

Case 8: Pot-bellied Rabbit

A weanling rabbit was brought to a veterinary clinic for examination. The rabbit had a firm but distended upper abdomen and was cachectic. There were no abnormal intestinal sounds or diarrhea.

a. What diagnostic procedures would contribute to making an accurate diagnosis?
b. Eventual necropsy examination of the rabbit revealed an enlarged liver that contained numerous raised pale yellow foci. How could you differentiate hepatic coccidiosis from cysticercosis (Taenia pisiformis) and tularemia?
c. What is the causative organism of hepatic coccidiosis?

Case 9: Maternal Neglect by a Doe

A primiparous (first litter) doe had a long, difficult delivery. Shortly after kindling, she partially cannibalized several kits, abandoned some, and nursed a few.

a. What causes cannibalism of newborn rabbits?
b. How can such behavior be prevented?
c. What may cause a doe to abandon her young?

Case 10: Death of a Pregnant Doe

An obese, 3-year-old, pregnant (27 days) doe that had died suddenly was submitted for necropsy examination. The rabbit had been fed table scraps and cow's milk. Gross lesions included multifocal, small (1–2 mm) pits on the renal surface, 10 dead fetuses, a light tan liver, and mineralized arteries.

a. What agent is the probable cause of the renal pitting? How is this agent transmitted? Did this agent contribute to the animal's death?
b. What is the probable cause of death and what is the pathogenesis of this condition? What husbandry steps might prevent or reduce the incidence of this disease in a rabbitry?
c. How long is the rabbit's gestation period?

Case 11: Foul-smelling Diarrhea in Does

An owner of a herd of 60 does reported the death of 17 does and an unspecified number of weanlings within a 12-hour period. Affected adult and weanling animals developed dull,

watery eyes, weakness, and incoordination, but the most prominent sign was a fulminating, smelly diarrhea. Body temperatures in terminal cases were between 40 °C and 41 °C.

a. Which conditions are probable differential diagnoses in this case?
b. What diagnostic procedures would you use to determine the cause of enteropathies in the does?
c. What would you do to prevent further devastation of this valuable breeding herd?

Case 12: Multiple Skin Ulcers in a Pet Rabbit

A pet rabbit has an ulcerated area on his nose that constantly exudes serous fluid. As the fluid dries, the lesion becomes crusted, and after a week the crust looked like a small horn. The crust can be removed, but a raw, moist, ulcerated surface remains. The rabbit also has several small scabs and crusts on the penis and scrotal pouches and several small crusted nodules on the lips. Treating with chlorhexidine and triple antibiotic ointment was not effective. Culture of plucked hairs from the edge of the lesions did not result in growth on D.T.M. media, and scrapings examined for mites were negative.

a. Which diseases should be considered in the differential diagnosis and what further diagnostics should be performed?
b. What should be done to establish a definitive diagnosis?
c. What treatment do you recommend?

Case 13: Aggression in Male Rabbits

A woman brought three intact adult male rabbits into the veterinary clinic. All three rabbits were cagemates and had recently started chewing on their fur and biting one another over the back and around the scrotum. Examination of stool specimens revealed an absence of internal parasites. The animals were destined for adoption as pet animals.

a. What dietary deficiencies may induce fur chewing?
b. Is the housing situation a factor in the chewing and biting?
c. What surgical procedures would you recommend?

Case 14: Facial Problems in a Buck

An adult male rabbit was submitted for necropsy examination. The animal had a purulent conjunctivitis, rhinitis, and a wet chin and dewlap with sticky, matted fur.

a. What are the causes of wet dewlap? How is this condition prevented and treated?
b. How would a P. multocida organism reach the orbit from the nasal passage?
c. How would you treat the conjunctivitis?

Case 15: Posterior Paresis in a Doe

A 2-month-old doe was submitted with a feces-soiled perineum. The attending clinician noted that the animal was dragging the rear limbs.

a. What is the differential diagnosis for the paresis? How would you proceed to a definitive diagnosis?
b. What is the probable explanation for the fecal staining of the perineum?
c. In cases of spinal luxation, what factors determine a recommendation of cage rest or euthanasia?

Case 16: Unthrifty Rabbit

A 7-year-old, intact, male New Zealand white rabbit presented to a veterinary clinic with a 2-month history of weight loss and a 2-week history of being off feed. The owner indicated that the animal had been seen previously by another veterinarian for chronic respiratory disease for which it had been treated with tetracycline in the water for the past 2 years.

On physical examination, the animal was lethargic and depressed with sticky mucous membranes, flaccid muscle tone, and a poor hair coat. A CBC and clinical chemistry panel reveal the following profile for this animal (normal reference range values for parameters are indicated in parentheses):

PCV	19%	(33–50%)
TP	74 g/dL	(54–83 g/dL)
Ca	3.0 mM	(1.4–3.1 mM)
P	3.4 mM	(1.3–2.2 mM)
Gluc	5.6 mM	(4.2–8.7 mM)
Creat	689.5 µM	(131–155 µM)
BUN	191 mg/dL	(3.6–6.9 mg/dL)
Na	151 mM	(131–155 mM)
K	6.4 mM	(3.6–6.9 mM)
ALT	63 U/L	(48–80 U/L)
Urine SG	1.010	(1.003–1.036)

a. What is your tentative diagnosis for this case? Is the condition acute or chronic? What evidence do you have from the profile?
b. What are your plans for treating this animal?
c. What is the prognosis for this animal?

THE GUINEA PIG

Case 17: Increased Appetite and Weight Loss in a Guinea Pig

A 4-year-old female guinea pig is presented for increased appetite and activity despite noticeable weight loss. The owner describes the guinea pig as a voracious eater and hyperactive. The change in appetite and activity began about 5–6 months ago.

a. What is your top differential diagnosis for this presentation?
b. What do you expect to find on physical examination and what diagnostic tests do you offer?
c. What treatment options are available for this disease in guinea pigs?

Case 18: Abdominal Pain in a Guinea Pig

A 3-year-old male guinea pig is presented because it is hunched and appears to be in pain. Radiographs are obtained (see Figure 6.1).

a. What is your radiographic diagnosis?
b. What is the most likely cause of this condition?
c. What is the treatment of choice?
d. What is the prognosis?

Case 19: Soft Stool in Guinea Pigs

A young male guinea pig had a 3-week history of persistent soft stool and lethargy. The animal remained thin despite the owner's attempts to improve the diet and enhance growth. After 3 weeks, the guinea pig died and was submitted to a veterinary clinic for evaluation. Necropsy revealed mucosal reddening within the ileum, cecum, and colon and a brown, watery content with no evidence of blood. Microscopically, there was moderate villous blunting and fusion in the distal small intestine; however, no Tyzzer's bacilli were observed.

a. What diseases should be considered in the differential diagnosis of cases involving soft feces in young guinea pigs?
b. Cryptosporidium spp oocysts were found in the guinea pig's feces. What does Cryptosporidium spp look like? Describe the technique for finding this organism in the feces.
c. How is Cryptosporidium spp transmitted? Is it a zoonotic disease?

Case 20: Fatal Pneumonia in Guinea Pigs

A local pet store received a shipment of 30 2-year-old, mixed-sex guinea pigs. Within 3 days of delivery, two animals developed respiratory distress, crusty eyelids, rough hair coat, depression, and anorexia, and died 4 days later. Necropsy examination revealed pulmonary consolidation and purulent exudates in the upper and lower airways.

a. What bacteria should be considered as possible etiologic agents for this disease outbreak? What are predisposing factors?
b. How could this outbreak have been prevented?
c. What therapy should be administered for the remaining animals? What is the prognosis for these animals?

Case 21: Mistreatment of Scurvy

A companion guinea pig was brought to a veterinary clinic. The animal exhibited joint swelling and had a history characteristic of an animal with scurvy, including vocalization when being picked up and food refusal. The veterinarian dispensed vitamin drops containing vitamin C adequate to eliminate hypovitaminosis C. After 2 weeks, the guinea pig was returned to the clinic with new problems. Despite a good appetite, the animal had become very thin and had lost most of its hair, although the obvious signs of scurvy had receded.

a. Which vitamin product might the veterinarian have prescribed or the client mistakenly purchased?
b. When is supplemental (in addition to that in the feed) vitamin C recommended for guinea pigs? How much is given daily?
c. What enzyme do guinea pigs lack that predisposes them to scurvy?

Case 22: Guinea Pigs with "Lumps"

Sporadic deaths occurred in 25 of 40 guinea pigs participating in a 4H club exhibition at a county fair. The clinical signs

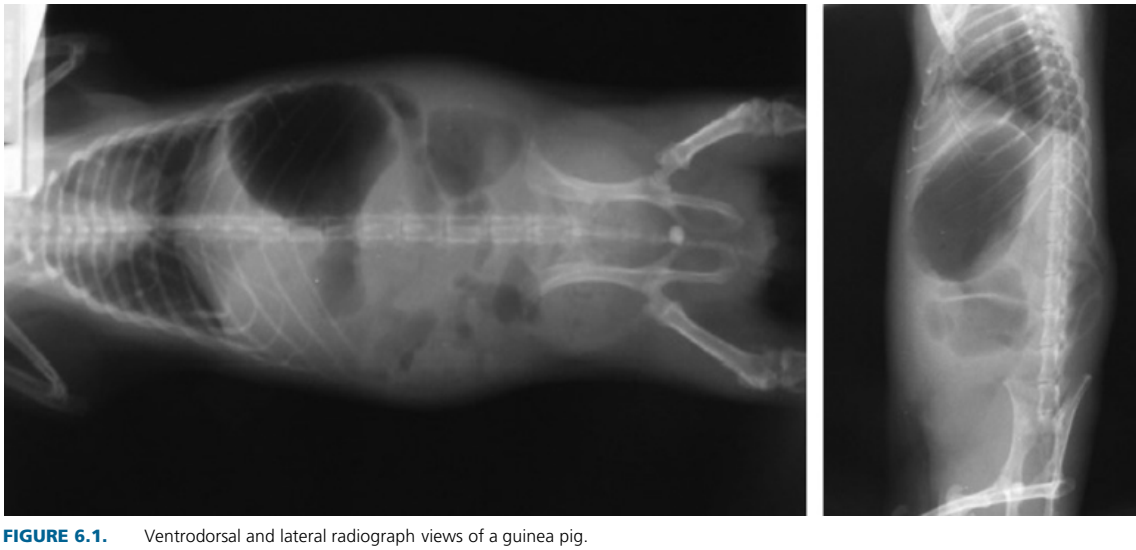


FIGURE 6.1. Ventrodorsal and lateral radiograph views of a guinea pig.



FIGURE 6.2. Severe bilateral pododermatitis of the hind feet in a guinea pig.

reported by the various owners included submandibular swellings in several animals and dyspnea in many. Necropsy signs included conjunctivitis, enlarged cervical lymph nodes, pneumonia, pleuritis, otitis media, and metritis.

a. Which pathogenic bacterium is probably involved?
b. This agent caused abortions in contact animals. What other factors may produce abortions or stillbirths in guinea pigs?

Case 23: Septicemia in a Guinea Pig

A student submitted a 600-g female guinea pig with a recent history of anorexia and peracute death. Gross necropsy examination revealed atelectasis and consolidation of the entire left lung and congestion and focal abscessation of the right lung. The spleen was enlarged and had several white foci on the capsular surface. Bilaterally, multifocal white foci were present on the capsular surface of the kidneys.

a. The lesions in this guinea pig indicate a septicemia. The enlarged spleen with the necrotic foci is suggestive of which diseases?
b. Is diarrhea a frequent finding in acute salmonellosis in small mammal pets?
c. What prognosis can be given for colonies with endemic salmonellosis?

Case 24: Swollen Feet in a Guinea Pig

A guinea pig weighing 1,500 g with marked painful swelling, ulceration, and crusting of the plantar surface of both hind feet was noted in a breeding colony (see Figure 6.2).

a. What factors predispose to pododermatitis in guinea pigs?
b. What complications may occur?
c. What treatments would you recommend?

Case 25: Consequences of Mastitis

A 620-g guinea pig sow, which had delivered two pups 5 days previously, was submitted for clinical examination. The right mammary gland was swollen and discolored, but the animal was otherwise bright and alert. The referring veterinarian treated the guinea pig with an injection of amoxicillin and the animal was sent home.

a. What are the likely causes of mastitis in guinea pigs? How should this condition be treated in sows?
b. The guinea pig died 3 days after the amoxicillin injection. What was the probable cause of death?
c. What provisions should be made for the orphaned 8-day-old pups?

Case 26: Stillbirths and Mortality in a Guinea Pig Breeding Colony

Ten guinea pigs were presented for evaluation from a pet store breeding colony with a recent history of increased mortality in near-term sows, stillbirths, and perinatal mortality in neonates. No significant gross lesions were seen at necropsy. Histologic evaluation revealed numerous intranuclear eosinophilic inclusions in mandibular salivary gland ductular epithelial cells of two of the sows (see Figure 6.3).

a. What virus produces characteristic inclusions in the mandibular salivary gland ductular epithelium of guinea pigs? What are other potential rule-outs for this case?
b. What clinical signs are usually associated with this viral infection in guinea pigs?
c. Is this a zoonotic infection?

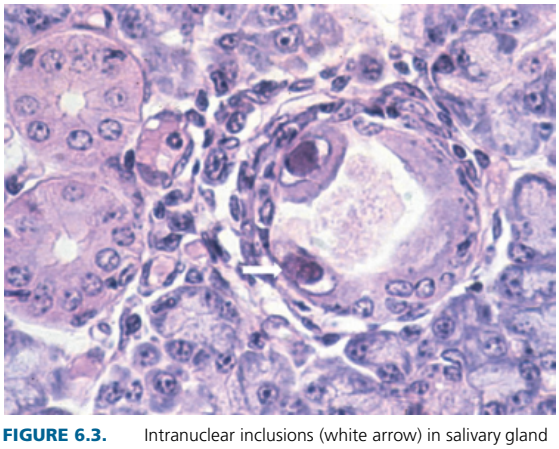


FIGURE 6.3. Intranuclear inclusions (white arrow) in salivary gland ductal epithelial cells from a guinea pig.



THE CHINCHILLA

Case 27: Head Tilt in a Chinchilla

An 11-year-old pet chinchilla was brought to a veterinary clinic because the owner had noticed the head was tilted to the right. The veterinarian also noted the right ear and lip were droopy. The chinchilla had been normal until a couple of days before and usually spent a lot of time outside of its cage, enjoying jumping on furniture and banking off walls. Skull radiographs were obtained (Figure 6.4).

a. What abnormalities are visible on the skull radiograph?
b. What is the likely cause of the abnormalities seen on clinical examination and radiographs?
c. What are the differential diagnoses for head tilt in a chinchilla?

Case 28: Hair Loss in a Chinchilla

A 7-year-old chinchilla has several patches of hair loss on its face and neck. A child in the household has also developed a sore on the arm.

a. What is the most likely diagnosis and etiologic agent?
b. What treatment options are available?
c. What was the most likely source of infection in the chinchilla?

Case 29: Enteritis in a Chinchilla

A 3-year-old neutered male chinchilla was seen by a veterinarian for anorexia and diarrhea. The chinchilla had been taken to an emergency clinic 2 days previously for treatment of a cat bite and had received fluids, pain medication, and antibiotics, which the owner had been continuing at home. The chinchilla was now depressed, hunched, and had developed diarrhea. The chinchilla was normally fed a good-quality pellet, grass hay, and the occasional piece of apple or raisin as a treat; however, the owner reported that it had not been interested in eating for at least a day. The veterinarian also noted dehydration and pain on abdominal palpation.

a. What additional history might be important in determining the cause of the chinchilla's problem?
b. What is the treatment for this condition?
c. What is the prognosis?

Case 30: Abortion and Death in Chinchillas

A chinchilla rancher requested postmortem examination of two chinchillas, both of which had aborted before death. Of 64 females, 34 had died, many experiencing abortions prior to death. No clinical signs of disease other than loss of appetite were observed before death. The animals were fed a high-quality pelleted ration and were occasionally given raisins as treats. On postmortem examination, the animals were cachectic, anemic, and had multifocal, pinpoint white foci on the liver capsule and mesenteric lymph nodes, and on the serosa of the colon.

a. What are the differential diagnoses for this finding?
b. What other clinical signs could result from infection with this agent?
c. What is the most likely source of infection?
d. What management advice could be given to the owner?

Case 31: Heart Murmur in a Chinchilla

A 3-year-old female chinchilla was brought to you for a wellness exam. On auscultation, a grade III out of VI heart murmur is detected. No other abnormalities are noted. An echocardiogram is collected (Figure 6.5).

a. How common are heart murmurs in chinchillas?
b. What are the primary differential diagnoses for this case?



FIGURE 6.4. Ventrodorsal view of a chinchilla skull.

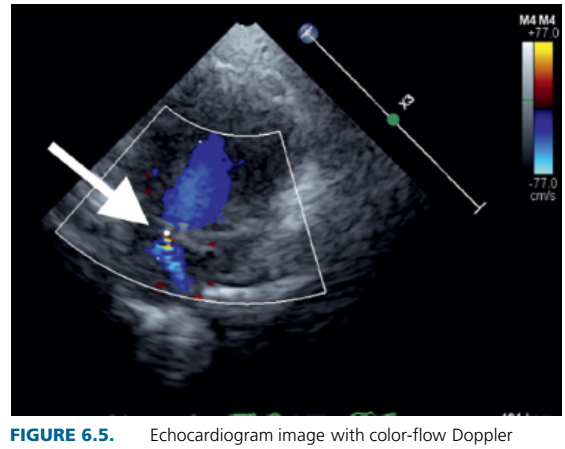


FIGURE 6.5. Echocardiogram image with color-flow Doppler revealing valvular regurgitation (white arrow) in a chinchilla with a grade III heart murmur.

c. What diagnostic tests would you recommend?
d. What signs should the owner monitor for in this animal?



THE HAMSTER

Case 32: Dermatitis in a Hamster

A 19-month-old companion male Syrian hamster developed alopecia and scabs over the back and rear limbs. The hairless area was pruritic and the hamster was observed to bite the affected area.

a. What are rule-outs for the condition described in this animal?
b. What diagnostics should be performed?
c. How would this case be treated?

Case 33: Hamster Alopecia

A 1-year-old pet golden hamster was reported to be losing hair for 2 weeks but was otherwise normal. The owner recently bought a new, larger cage for the hamster.

a. What are the differential diagnoses for nonpruritic alopecia in the golden hamster?
b. What diagnostic procedures should be undertaken to determine the cause of the hair loss?

Case 34: Fatal Enteritis in Hamsters

A pet store supplier is experiencing high mortality in his teddy bear hamster stocks. Seven of 25 animals have been found dead with no premonitory signs, and three have diarrhea and are huddling. Rats and mice housed in the same area are not demonstrating clinical signs. The animals are fed standard rodent chow and reared in fish tanks with wire lids and kept at the back of the store. Tanks are cleaned out weekly. Animals are obtained from other local suppliers and breeders approximately monthly. The owner agrees to bring in two of the sick animals for examination. You are presented with one weanling and one adult hamster that are hunched, dehydrated, and have unkempt hair coats. Both hamsters have perineal fecal staining and are moribund. You deeply anesthetize one animal, collect blood via a cardiac puncture, and perform a complete necropsy. Gross examination reveals a thickened ileum and multifocal white spots on the liver.

a. What additional tests would you recommend?
b. What is your provisional diagnosis and what therapy would you recommend?
c. What is the prognosis?

Case 35: Swollen Hamsters

Two laboratory hamsters from a group of five that are control animals in an infectious disease study present within 2 weeks of each other with severe subcutaneous edema (anasarca). The animals are 18-month-old SPF females that have been provided with routine husbandry. The other three animals look normal. The hamsters have been housed individually to avoid fighting.

a. What rule-outs will you consider and what diagnostics do you recommend? Are any therapeutics indicated?
b. What are common nonneoplastic, noninfectious diseases seen in aged hamsters?

Case 36: Abdominal Enlargement in a Hamster

A 3-year-old male Syrian hamster is presented for a gradual onset of abdominal swelling, lethargy, and lateral recumbency. By the time he reaches your practice, he is open-mouth breathing. The owner elects for euthanasia and allows you to do a necropsy.

a. What organs are you most interested in examining and why?
b. Large cystic structures in the abdomen are visualized. What organ are they most likely associated with?
c. What is the second most common organ affected by polycystic disease in hamsters?



THE GERBIL

Case 37: Skin Mass and Head Tilt in Gerbils

Two 4-year-old gerbils were brought to a veterinary clinic for examination. One gerbil had a soft, subcutaneous mass (1 × 2 cm) on the midventral abdomen posterior to the xiphoid process. An abscess was detected by aspiration. The abscess was drained and flushed, and the gerbil was given trimethoprim/sulfa in a cherry-flavored syrup and sent home. One month later the gerbil returned to the clinic with a firm mass in the same area. The second gerbil had developed a mild but fixed head tilt. This animal was treated successfully with corticosteroids and systemic antibiotics.

a. For the first gerbil, the abscess was a secondary problem. What primary disorder might be suspected?
b. Enrofloxacin and dexamethasone successfully stopped the progression of the torticollis in the second animal. What are potential differential diagnoses for head tilt in a gerbil? What is the therapeutic function of the steroid?

Case 38: Death of Young Gerbils

Two 17-day-old gerbils were presented to a veterinary clinic for necropsy examination. The gerbils were found to be cachectic and dehydrated, and the stomach of both animals had multifocal hemorrhages on the mucosal surface, consistent with acute ulceration. The dam and two other littermates were reportedly in good health. The diet provided was a high-quality, pelleted chow, and water was provided via a bottle with a sipper tube attached to the side of the cage.

a. At what age are gerbils weaned?
b. What husbandry conditions might have resulted in the death of the 2 littermates?

Case 39: Rough Hair in Gerbils

A family purchased a pair of 6-week-old gerbils. The family was hoping to breed the animals and requested general information about breeding gerbils from a veterinarian. The clients were also concerned about the gerbils' rough hair coats.

a. What causes gerbils to have rough hair coats?
b. How do you verify that the gerbils are a breeding pair?
c. What type of cage, feed, bedding, feeding, and watering devices, and nesting boxes should the practitioner recommend?

Case 40: Sudden Death in Gerbils

A young adult female gerbil and several weanlings died suddenly with no other clinical signs. The ileocecal–colonic junction was hyperemic, and the liver surface was seen to have multifocal pale white foci on the surface.

a. What common enteric condition of rabbits and rodents also causes focal hepatic necrosis?
b. How is the causative agent transmitted? Does it persist in the cage environment?
c. How would one obtain a specific diagnosis in this case?

Case 41: Ocular and Nasal Discharge in Gerbils

One animal of a pair of male gerbils developed a copious, red-brown purulent discharge from the left eye and nares. Adjacent skin and nose were hairless, moist, and erythematous. The swollen lids and pus covered the intact eyeball. *Staphylococcus aureus* was isolated in pure culture from the purulent material.

a. What is the most likely etiology of this condition?
b. What is the source or cause of the reddish-brown pigment in the pus?
c. How should this gerbil be treated?

Case 42: Abdominal Swelling in a Gerbil

A 3 year-old female gerbil is presented for bilateral abdominal swellings and lethargy. The breeder had also noted difficulty breathing, hair loss along the flanks, reduced food intake, and smaller litter sizes.

a. What are differential diagnoses for this case?
b. What diagnostic tests would you recommend?
c. What treatment options can you offer?

THE MOUSE

Case 43: Paresis in a Male Mouse

A male mouse developed a slowly progressive posterior paresis, diarrhea, and perineal swelling. This pet mouse had been taken from a cage containing another male mouse.

a. What is the probable cause of the clinical signs seen in this mouse?
b. What recommendations might be made to the owner to avoid this condition in pair- or group-housed male mice in the future?

Case 44: Fatal Disease in a Colony of Mice

Inbred C3H female mice were inoculated with mouse serum obtained from a commercial supplier as part of an immunization protocol. Over the next 3 weeks, all recipient mice died. Clinical signs, when they occurred, included a rough hair coat, facial swelling, conjunctivitis, and death.

a. What fatal diseases of mice should be considered in this outbreak?
b. What precautions should be taken to reduce the possibility of the spread of an infectious disease from this colony?
c. How could the disease be diagnosed?

Case 45: Prolapsed Rectums in Mice

Six young male mice, four alive and two dead, were emaciated and had soft, bloody feces around the anus. All mice had evidence of either catarrhal or hemorrhagic enteropathy and had grossly thickened colons. The livers of the animals were pale, and the spleens were enlarged. Two animals had prolapsed rectums. Culture of the colonic contents resulted in a heavy growth of *Proteus* spp. and coliform-like organisms.

a. Why did the mice have pale viscera?
b. What pathologic processes might account for the thickened colon?
c. What etiologic agents might be suspected in this case?
d. How would you contain an outbreak of enteritis in a large mouse colony?

Case 46: Diarrhea in Neonatal Mice

Ten 5- to 7-g 2-week-old mice with stunted growth, rough, fecal-stained hair coats, focal alopecia, and watery diarrhea were submitted for necropsy examination. The large intestine contained fluid feces. Several other litters in the room had died recently.

a. What viral conditions cause diarrhea in weanling mice? How would you differentiate these conditions?
b. What agents or processes might cause focal alopecia in mice?
c. What murine viruses are carried subclinically in the mouse gut?
d. Define morbidity. Define mortality.

Case 47: Itchy Mice

A client presents several mice from a colony that he raises in his basement to provide food for his snakes. He has noted hair loss, bleeding, and itching on most of the animals in the colony. On physical exam, you noted scabs and exudative dermatitis around the face and head. Animals were noticeably

pruritic. The client has not noted any unusual deaths, and both males and females of various ages were affected.

a. Given this history, what is the most likely diagnosis?
b. If animals were nonpruritic, males had scabs, and females had areas of alopecia without dermatitis, what conditions would you suspect?
c. What diagnostic tests would you perform? How do these exams differ from similar procedures in the dog or cat?
d. Assume you are able to diagnose your top rule-out. What would you use to treat the animals? What would you tell the client when he asks whether he can feed the sick animals or those under treatment to his snakes?



THE RAT

Case 48: Respiratory Disease in Rats

A client presented a 2-year-old male rat that has lost weight recently and become less active. Upon examination you note an unkempt hair coat, labored respiration, and red discharge from the eyes and nose. The rat weighs 300 g.

a. What is the normal weight range of an adult male rat?
b. What is the likely cause of the red discharge?
c. What diagnostic procedures are available to differentiate among the several organisms that might be involved in this case?
d. What is the most likely diagnosis, an appropriate therapy, and long-term prognosis?
e. What noninfectious diseases might be present in an animal with this signalment?

Case 49: Moveable Masses in Rats

A young girl brings two adult, female companion rats to the clinic. Both rats have single, 2-cm, firm, moveable, subcutaneous masses in the axillary region. Fibrous connective tissue cells are seen by fine-needle aspirates taken from the masses.

a. What is the probable origin of the masses?
b. What histologic type of neoplasm occurs most often in the mammary gland of the rat?
c. What is an appropriate treatment for this condition?
d. Are the masses likely to reoccur if they are removed?

Case 50: Sore Eyes in Rats

A colony of 40 Long-Evans rats housed in open-top caging experienced an outbreak of "squinting" eyes and sneezing associated with a serous conjunctivitis. The eyelids were swollen, and exudate matted the surrounding fur. After a week the outbreak subsided, although several rats had clouded corneas. Histopathologic examination of the Harderian glands revealed acute edematous inflammation, necrosis, and squamous metaplasia of the glandular epithelium. *Staphylococcus aureus* was recovered in pure culture from the conjunctival sac of three rats. No organisms were cultured from the conjunctiva of several other affected animals.

a. What is the hair color pattern of the Long–Evans rat?
b. What is the probable classification of the etiologic agent? How could it be definitively diagnosed?
c. Why would corneal damage occur?
d. What management practices could be instituted to prevent spread of the disease?

Case 51: Dermatitis in Rats

A rat that had been presented for spay returned to the clinic post procedure because of reddening of the dorsal skin along the length of the body. The animal had been anesthetized with isoflurane in oxygen during the procedure and had been warmed using a heating pad set on the low setting.

a. What is the most probable cause of the lesions?
b. How could the lesions be prevented?

Case 52: Rats With White Streaks in the Urinary Bladder

A feeder colony of rats is maintained for a small private zoo. The owners have noticed some sneezing among the rats and submitted several animals for necropsy evaluation. Following gross and histological examination, the only lesions noted are small thread-like white worms in the wall of the urinary bladder and parasitic larval forms with associated leukocytic infiltrates in the lungs.

a. What one parasite could cause both the respiratory and urinary tract abnormalities?
b. What laboratory tests can be conducted to provide confirming diagnostic evidence?
c. How can the condition be treated and eliminated from the colony?
d. Discuss the life cycle of this parasite.

SUGGESTED SOLUTIONS

The following answers to questions posed in the clinical cases are intended to emphasize the main points for each case and are not meant to include detailed discussions of each case or problem.



RABBITS

Case 1

a. The top differential diagnosis for this type of presentation in a companion rabbit is a liver lobe torsion. Rabbits with liver lobe torsion are frequently anemic and demonstrate

elevation of most liver enzymes (note that these enzymes are not specific for liver in rabbits).

b. The diagnosis can be confirmed readily with an abdominal ultrasound examination, (Figure 6.6) which shows a liver lobe with decreased echogenicity and poor-to-no-blood flow on color Doppler. Free fluid or perihilar fluid is also frequently seen. On an emergency basis, an abdominal-focused assessment with sonography in trauma (A-FAST) (Figure 6.7) evaluation (i.e., quick abdominal ultrasound examination) may also help to rapidly diagnose this condition if the torsed liver lobe is large enough by using color Doppler. The caudate lobe of the liver is the most frequently torsed lobe.

   Abdominal radiographs are insensitive for this disorder, but an increased radiodensity over the liver area may be observed on the lateral view. The condition also can be diagnosed with a contrast CT scan of the abdomen, as the torsed liver lobe will fail to pick up contrast compared to the other lobes.

c. The treatment of choice is surgery via a laparotomy and hepatic lobectomy. If necessary, rabbits should be stabilized for a few hours before the surgery, if possible. Giving intravenous fluids, pain medication (fentanyl CRI, for example), and administering a vasopressor (norepinephrine) before and during surgery will improve the prognosis. In some cases, rabbits recover without surgery, but medical treatment should only be attempted in cases where financial constraints prevent the surgical option. The prognosis with surgery is fair.

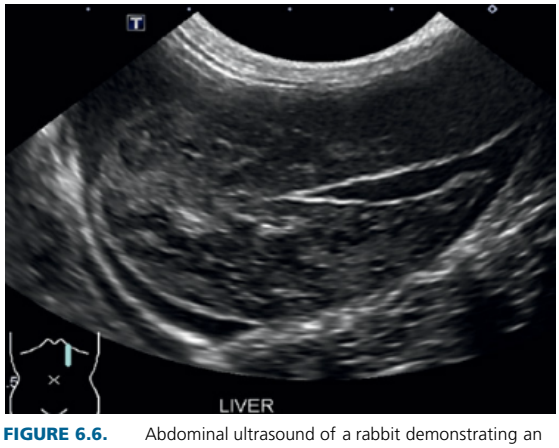


FIGURE 6.6. Abdominal ultrasound of a rabbit demonstrating an enlarged hypoechoic liver lobe with rounded margin suggestive of liver lobe torsion.

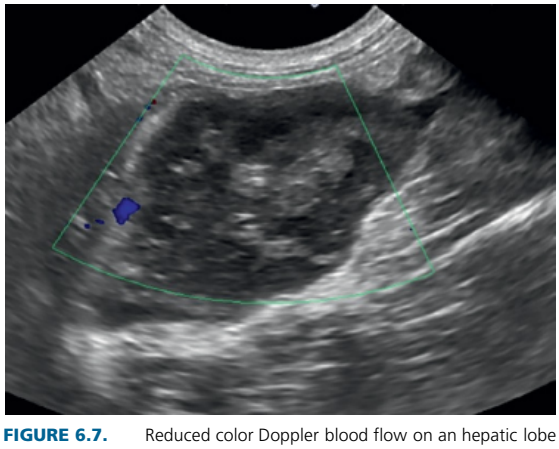


FIGURE 6.7. Reduced color Doppler blood flow on an hepatic lobe suggestive of liver lobe torsion in a rabbit.

Reference

Graham J, Basseches J. Liver lobe torsion in pet rabbits: clinical consequences, diagnosis, and treatment. Vet Clin North Am Exot Anim Pract 2014, 17:195–202. 10.1016/j.cvex.2014.01.004.

Case 2

a. This is the typical presentation of thymoma in rabbits. A thymoma is a tumor derived from the epithelial cells of the thymus. The large mediastinal mass presses on adjacent structures, such as the trachea, resulting in dyspnea, impairing venous return, and resulting in bulging eyes in rabbits (or prolapse of the third eyelids) as well as displacing the heart resulting in muffled heart sounds. Other differential diagnoses for a cranial mediastinal mass include thymic lymphoma and thymic carcinoma, both of which are much less common.

b. Radiographs typically show a large cranial mediastinal mass that tends to dorsally displaced the trachea. The mass is poorly delineated on radiographs (Figure 6.8). and more clearly seen in a CT scan (Figure 6.9).

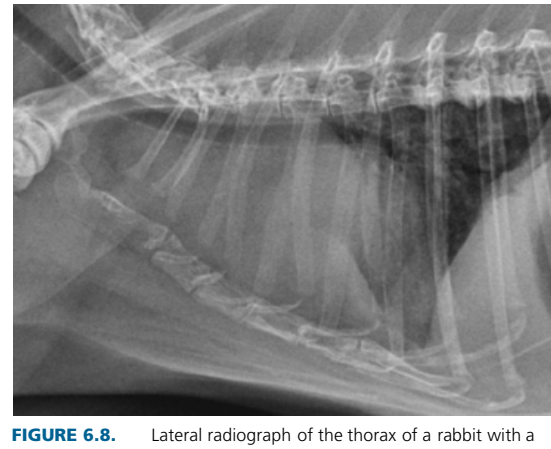


FIGURE 6.8. Lateral radiograph of the thorax of a rabbit with a large cranial mediastinal mass (thymoma). A CT scan allows accurate diagnosis and characterization of the mass and heart displacement.



FIGURE 6.9. Sagittal view from a contrast CT scan of a rabbit with a thymoma. A thoracic ultrasound can also help to outline the mass and allow for ultrasound-guided fine-needle aspirate. Cytology of these aspirates is often diagnostic.

c. The best treatment option for rabbit thymoma is radiation therapy. Palliative or curative protocols have been employed and are typically very effective in rabbits and well tolerated. The median survival time with radiation therapy is 1–2 years. Surgical removal is possible, but is associated with a poor prognosis as the surgery is invasive and not well tolerated by rabbits. Surgery involves a thoracotomy with excision or debulking of the mass. Chemotherapy is another option, but efficacy tends to be much lower than treatment with radiation therapy and is associated with more adverse effects. Only anecdotal information is available on the use of chemotherapy in the treatment of thymomas in rabbits. Prednisone can be used as a palliative treatment.

References

Andres KM, Kent M, Siedlecki CT, Mayer J, Brandão J, Hawkins MG, et al. The use of megavoltage radiation therapy in the treatment of thymomas in rabbits: 19 cases. Vet Comp Oncol 2012, 10:82–94. 10.1111/j.1476-5829.2011.00273.x.

Künzel F, Hittmair KM, Hassan J, Dupré G, Russold E, Guija de Arespachochaga A, Fuchs-Baumgartinger A, Bilek A. Thymomas in rabbits: clinical evaluation, diagnosis, and treatment. J Am Anim Hosp Assoc 2012, 48:97–104. 10.5326/JAAHA-MS-5683.

Case 3

a. Bacterial encephalitis, poisoning, enterotoxemia, rabies, nutritional deficiencies, heat stroke, encephalitozoonosis, toxoplasmosis, and nematode migration (*Baylisascaris procyonis*) in the brain should be included among the differential diagnoses.

b. Definitive ante mortem diagnosis is difficult. Serology can be used to help rule out *Encephalitozoon* spp., and an MRI or CT scan can help to differentiate the pathologies caused by each agent. Culture and isolation and special stains of affected tissues can be used to search for a specific cause postmortem. Encephalopathies due to *E. cuniculi* should be ruled in or out by examining histologic sections of the brain and kidney.

c. Rabbits may be infected with *Toxoplasma gondii* by ingesting grass contaminated with cat feces containing oocysts shed by feral cats. Only cats have been recognized to support all life phases of *T. gondii*. The organism can be transmitted transplacentally in rabbits and other animal species. *Encephalitozoon cuniculi* is usually transmitted in early life from dam to offspring. *Baylisascaris* spp. larval migrans results when rabbits graze in areas that are contaminated with fecal oocytes shed by raccoons or skunks. Oocytes are shed in very high numbers by these species and are highly resistant to desiccation in the environment (Figure 6.10).

d. Pregnant women and individuals with a compromised immune system should be apprised of the high zoonotic potential of toxoplasmosis when oocysts are shed into the environment by cats. Humans are also susceptible to *Baylisascaris* spp. larval migrans. The condition is most common in children, who may ingest dirt or play in areas in which cats, raccoons, and other species may defecate. Both toxoplasmosis and *Baylisascaris* spp. infection require ingestion of oocysts in the environment. Although rabbits do not shed oocysts when infected by *T. gondii*, infection can also be transmitted when undercooked rabbit meat containing cysts is consumed. A thorough history and clinical evaluation are very important in confirming the diagnosis and in the execution of preventive measures.

e. Without a specific diagnosis, symptomatic therapy can be instituted. This would include hand feeding and watering, consideration of steroid therapy and broad spectrum antimicrobials, and albendazole for treatment of potential parasitic disease. The prognosis is guarded.

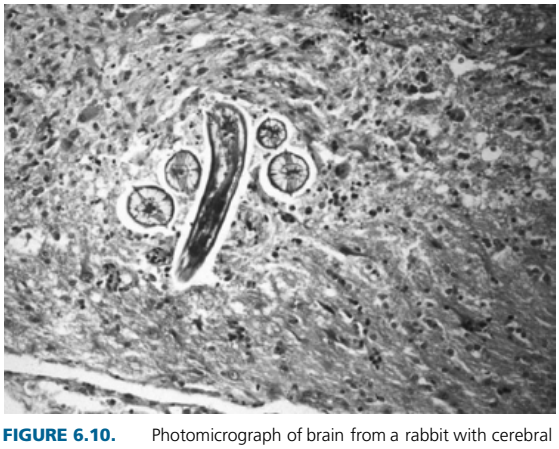


FIGURE 6.10. Photomicrograph of brain from a rabbit with cerebral larval migrans due to *Baylisascaris procyonis*. Several sections of the larva can be seen.

References

Deeb BJ, DiGiacomo RF. Cerebral larva migrans caused by Baylisascaris sp. in pet rabbits. J Am Vet Med Assoc 1994, 205(12):1744–1747.

Dubey JP, et al. Fatal toxoplasmosis in domestic rabbits in the USA. Vet Parasitol 1992, 44:305–309.

Furuoka H, Sato H, Kubo M, et al. Neuropathological observation of rabbits (*Oryctolagus cuniculus*) affected with raccoon roundworm (*Baylisascaris procyonis*) larva migrans in Japan. J Vet Med Sci 2003, 65(6):695–699.

Harcourt-Brown FM, Holloway HK. Encephalitozoon in pet rabbits. Vet Rec 2003, 152(14):427–431.

Leland MM, Hubbard GB, Dubey JP. Clinical toxoplasmosis in domestic rabbits. Lab Anim Sci 1992, 42:318–319.

Case 4

a. Vitamin A deficiency or excess can provoke release of hydrolases as a result of compromised structural and functional integrity of cellular lysosomes. In particular, excess vitamin A promotes decreased plasma and liver vitamin E levels, which can contribute to reproductive problems. Vitamin E is an essential dietary substance that protects cellular membranes and organelles from endogenous peroxidation. Kidney, plasma, and liver samples may be analyzed for vitamins A and E levels.
b. Deficiency of vitamin A or other nutrients can result from general malnutrition or anorexia stemming from illness. Infrequently, deficiency and excess of vitamin A is the result of an improperly formulated ration, as in this case. To confirm this diagnosis, analysis of feed should be conducted in conjunction with consideration of response to management changes and therapeutic supplementation or reduction of the vitamin in question.
c. Hypervitaminosis A can lead to follicular hyperkeratosis, anemia, increased susceptibility to infection and cancer, and night blindness. Toxicities involving arsanilic acid, DDT, nitrates, various mycotoxins such as zearalenone and aflatoxin, infections such as listeriosis, salmonellosis, aspergillosis, chlamydiosis, and other less well-defined conditions such as systemic disease and colony overcrowding should be included in the differential diagnoses of reproductive disorders in rabbits. The recovered *P. multocida* is probably an opportunistic invader responding to the retained and dead fetuses along with the uterine pathology associated with the vitamin imbalance.
d. The most likely diagnosis is hypervitaminosis A or, less likely, hypovitaminosis E.

References

DiGiacomo RF, Deeb BJ, Anderson RJ. Hypervitaminosis A and reproductive disorders in rabbits. Lab Anim Sci 1992, 42:250–254.

Hafez AH, Gomma A, Mousa SA, et al. Aflatoxin and aflatoxicosis. IV. The effect of dietary aflatoxins on adult fertile male and female rabbits at various reproductive conditions. Mycopathologia 1983, 83:183–186.

Ismail AM, et al. Hypervitaminosis A in rabbits. I. Dose response. J Appl Rabbit Res 1992, 15:985–994.

Yamini B, Stein S. Abortion, stillbirth, neonatal death, and nutritional myodegeneration in a rabbit breeding colony. J Am Vet Med Assoc 1989, 194:561–562.

Case 5

a. The probable cause is urinary tract obstruction by a urolith and an associated hemorrhagic cystitis. The cause of urolithiasis in rabbits is not known, but it may be associated with chronically elevated plasma calcium levels, excessive vitamin D intake, and almost certainly other factors. Other rule-outs in this case would include uterine adenocarcinoma, ruptured endometrial aneurysms, and mummified fetuses. Porphyrinuria, or accumulation of porphyrin pigments in the urine, should also be considered.
b. Treatment involves a cystotomy and removal of the urolith, or uropropulsion in the case of "bladder sludge," follow-up antimicrobial therapy (e.g., trimethoprim/sulfa), dietary adjustments, and resolution of dehydration and anorexia. Acidification of rabbit diets to prevent recurrence of stones should not be attempted because rabbits are herbivores, and consequently, their urine is normally basic; considerable acidification would be required to achieve an aciduria.
c. Dietary recommendations include providing a lower calcium diet by feeding fewer pellets, which are typically high in calcium and more grass hay, which is usually lower in calcium. Water should be provided at all times.

References

Garibaldi BA, Pecquet-Goad ME. Hypercalcemia with secondary nephrolithiasis in a rabbit. Lab Anim Sci 1988, 38:331–333.

White RN. Management of calcium ureterolithiasis in a French lop rabbit. J Small Anim Pract 2001, 42(12):595–598.

Case 6

a. Conjunctival overgrowth or hyperplasia. This is an unusual abnormality unique to the rabbit, in which conjunctival tissue grows across the sclera onto the cornea. It has also been called pseudopterygium, aberrant conjunctival stricture, conjunctival centripetalization, precorneal or epicorneal membranous occlusion, and circumferential conjunctival hyperplasia.
b. Treatment involves making several incisions into the overgrowing conjunctiva from the free edge to the limbus followed by transpalpebral fixation to restore the conjunctival fornix.
c. The prognosis is good if the conjunctival tissue is sutured as described above. Prognosis is guarded if the tissue is simply trimmed away, as recurrence is common.

References

Allgoewer I, et al. Aberrant conjunctival stricture and overgrowth in the rabbit. Vet Ophthalmol 2008, 11:18–22.

Katsuta O, et al. Pseudopterygium: unique conjunctival stricture observed in Japanese White rabbit. J Toxicol Pathol 2008, 21:239–241.

Case 7

a. Traumatic spinal or limb injury, inherited defects, infectious diseases, toxin effect, metabolic upset, and neuromuscular disease can cause ataxia.
b. A common cerebral disease of rabbits is encephalitozoonosis, but clinical signs are rare. Cerebral nematodiasis also can cause incoordination.
c. The brain and kidneys are tissues to be examined. A Gram stain will be positive for *E. cuniculi*, while a PAS reaction is less predictive for rabbit strains of the organism.

Reference

Künzel F, Fisher PG. Clinical signs, diagnosis, and treatment of *Encephalitozoon cuniculi* infection in rabbits. Vet Clin North Am Exot Anim Pract 2018, 21:69–82. 10.1016/j.cvex.2017.08.002.

Case 8

a. Diagnostic procedures to determine the cause of a distended abdomen and cachexia in the rabbit would involve palpation, radiography, or ultrasonography for intestinal distention, hepatomegaly, and a gastric hair ball. The oral cavity should be examined for malocclusion and the feces for coccidial oocysts.
b. In hepatic coccidiosis, the lesions are linear and irregular (they follow the bile ducts) with indistinct margins. A smear of a cut section of the liver or gallbladder would reveal oocysts on microscopic examination. *Taenia* cysticercus lesions are usually rounded and have distinct margins. Larval cysts may be present in the peritoneal cavity. The miliary white foci of necrosis caused by *Francisella tularensis* will occur throughout the abdominal parenchyma and not just the liver. Tularemia is rare in domestic rabbits but more common in wild rabbits, especially in tick-infested areas.
c. *Eimeria stiedae* is the causative organism of hepatic coccidiosis in rabbits.

Reference

Wilkinson MJ, Bell S, McGoldrick J, Williams AE. Unexpected deaths in young New Zealand white rabbits (*Oryctolagus cuniculus*). Contemp Top Lab Anim Sci 2001, 40:49–51.

Case 9

a. Cannibalism of neonatal rabbits has been associated with prolonged delivery, poor nest building, chilling of young, hereditary nervousness, consumption of placentas, disturbance of the doe, presence of abnormal or dead young, water deprivation, improper nest box design, low caloric diets, and a myriad of other factors difficult to define.
b. Correct any of the previously listed deficiencies. Keep the doe calm at kindling time. Place the hutch and nesting box away from loud or unusual noises, strangers, and predators (snakes, opossums, raccoons, foxes, coyotes, dogs, cats, and other feral animals). Fresh drinking water and a sufficient amount of food should be provided. Mortality may decrease if the doe–kit contact is restricted to one 15- to 30-minute daily nursing session. Does that cannibalize successive litters should be culled.
c. If a rabbit nest is split or if one or more young is out of the nest, the doe may not retrieve and combine the young. Some stimuli—for example, low body temperature of the neonate, odor, or a behavioral or physical abnormality—may cause rejection.

References

González-Redondoa P, Zamora-Lozano N. Neonatal cannibalism in cage-bred wild rabbits (*Oryctolagus cuniculus*). Arch Med Vet 2008, 40:281–287.

Rödel HG, Starkloff A, Bautista A. Infanticide and maternal offspring defence in European rabbits under natural breeding conditions. Ethol 2008, 114:22–31.

Rödel HG, von Holst D, Kraus C. Family legacies: short- and long-term fitness consequences of early-life conditions in female European rabbits. J Anim Ecol 2009, 78:789–797. 10.1111/j.1365-2656.2009.01537.x.

Case 10

a. The renal lesion may be a manifestation of interstitial nephritis caused by *E. cuniculi* (passed in the urine). Infection with this agent is usually asymptomatic, though CNS symptoms can occur.
b. Pregnancy toxemia (acidosis) is the probable cause of death and is related to mobilization of fats during times of high-energy demand. Obese animals and those on poor diets are at higher risk. Some causes of pregnancy toxemia or ketosis are prevented by eliminating obesity in breeding does through reduced food intake or feeding high-fiber feed. The underlying defect may be inadequate nutrients reaching the fetuses because of damaged uterine vessels.
c. The rabbit's gestation period is between 28 and 34 days.

Reference

Brower M. Practitioner's guide to pocket pet and rabbit theriogenology. Theriogenol 2006, 66:618–623.

Case 11

a. Clostridial enterotoxemia is a probable diagnosis. Rotavirus infection, Tyzzer's disease, colibacillosis, or coccidiosis should be considered also.
b. Clinical history, a fecal examination for coccidial oocysts, necropsy examination, determination of enterotoxin or centrifugation of cecal content for cytological evaluation of *Clostridium spiroforme* and culture might provide a diagnosis. A specific diagnosis is usually difficult to determine.
c. The prognosis is poor. Higher fiber feed should be provided, along with fluid therapy, but the fatal event is probably an enterotoxemia. Symptomatic therapy may save a few animals. Prevention of recurrence includes strict sanitation,

reduction of stress, provision of higher fiber feed, selection of *Clostridium*-free breeding rabbits, and cessation of practices that affect rapid changes in the quantity of feed consumed. Pregnant does on restricted feeding should gradually be introduced to full high-energy feed after kindling.

References

EFSA Panel on Animal Health and Welfare (AHAW), et al. Assessment of animal diseases caused by bacteria resistant to antimicrobials: rabbits. EFSA J 2021, 19:e06999. 10.2903/j.efsa.2021.6999.

Perkins SE, Fox JG, Taylor NS, et al. Detection of *Clostridium difficile* toxins from the small intestine and cecum of rabbits with naturally acquired enterotoxemia. Lab Anim Sci 1995, 45:379–384.

Case 12

a. Differential diagnoses should include rabbit syphilis, caused by *T. pallidum*, myxomatosis, bacterial dermatitis, and neoplasia (Shope fibroma, papilloma, or squamous cell carcinoma). The last three rule-outs should be considered but are less consistent with the clinical presentation. Dermatophytosis and ectoparasitism cannot be entirely ruled out even though initial diagnostics were negative.
b. These are classic lesions of rabbit syphilis and further testing may be unnecessary. Biopsy and histopathologic examination, impression smear evaluation for spirochetes, and serologic tests for syphilis could be conducted.
c. Penicillin, 50,000–200,000 IU per 4.5 kg BW, administered intramuscularly for 3 days, is recommended, and works well, although penicillin administered orally may cause fatal enterotoxemia. Amoxicillin and ampicillin should never be used orally or parenterally in rabbits.

References

Jekl V, Nováková M, Jeklová E, Pospíšilová P, Křenová J, Faldyna M, et al. Penicillin treatment failure in rabbit syphilis due to the persistence of treponemes (*Treponema paraluisleporidarum Ecovar Cuniculus)* in the focus of infection. Front Vet Sci 2021, 8:675631. 10.3389/fvets.2021.675631.

Varga M, Paterson S. Dermatological Diseases of Rabbits. In: Quesenberry KE, Orcutt CJ, Mans C, Carpenter JW. Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery. St. Louis, MO: Elsevier, 2020. p. 220–232.

Case 13

a. Fur chewing may indicate a fiber deficiency or a stress response. Selectively altering protein, salt, fiber (hay), or MgO (5 lb/ton of feed) in the diet and making certain that potable drinking water is available may eliminate the fur-chewing problem. Rabbits and other species may ingest fur or other high-fiber materials to decrease pain from acute enteritis.
b. Housing sexually mature male rabbits in separate cages will reduce or eliminate fur-chewing behavior and will eliminate biting and fighting. Alternatively, providing hiding places and escape routes for group-housed rabbits will permit more subordinate animals to escape the unwanted attentions of dominant rabbits.
c. These rabbits should be neutered to improve behavioral attributes as pets and to decrease incidence of reproductive diseases as they age.

Reference

Bradley T. Rabbit care and husbandry. Vet Clin North Am Exot Anim Pract 2004, 7:299–313, vi.

Case 14

a. Drooling or ptyalism in rabbits may be caused by malocclusion, or the dewlap may become wet and abraded if the rabbit feeds or drinks from crocks. Obese females are predisposed to this condition. A wet dewlap, often associated with a moist, bacterial dermatitis, may be prevented by correcting malocclusion or by feeding from hopper feeders and watering through sipper tubes rather than crocks or bowls. Superficial, moist dermatitis is treated by shaving the hair over the lesion, cleansing the skin with an antiseptic soap, rinsing, and applying a topical antibiotic powder or ointment.
b. *P. multocida* may reach the conjunctival sac from the nasal cavity via the nasolacrimal duct or by transmission on the forepaws from the nares.
c. Conjunctivitis in rabbits may be treated with an ophthalmic ointment containing an antibiotic or by systemic antibiotics. Treatment of the conjunctival infection does not necessarily eliminate the organism in the nasal passage. Flushing of the nasolacrimal duct with saline and then an antibiotic solution will reduce bacterial numbers and allow conjunctival exudate to drain to the nasal area and thus reduce matting of hair around the eye. Underlying causes of the conjunctivitis, including tooth root abscesses, should be investigated.

Reference

Rougier S, Galland D, Boucher S, et al. Epidemiology and susceptibility of pathogenic bacteria responsible for upper respiratory tract infections in pet rabbits. Vet Microbiol 2006, 115:192–198.

Case 15

a. A congenital abnormality involving the spine, coxofemoral junction, or rear limb bones may exhibit a familial inheritance pattern (i.e., splay leg), or the condition may be associated with flooring with poor traction during limb development. A traumatic injury would have a history of sudden onset and an association with a fall, improper restraint, or other traumatic event in most cases. Rabbits with hypovitaminosis E may not be able to use their rear limbs because of dystrophic muscles. A definitive diagnosis would be established by thorough history and physical examination, including neurologic examination and imaging studies.
b. Neurologic control of defecation and urination is often impaired following traumatic lumbosacral dislocation or luxation due to damage to the spinal cord. Increased

soiling also occurs if animals are dragging their rear legs due to neurological impairment.

c. The prognosis of posterior paresis in the rabbit depends on the extent of the damage to the vertebral column, spinal cord, and nerve trunks. If the lesion is due to focal spinal cord edema and inflammation, cage rest for 7–10 days and use of drugs to reduce edema and inflammation (i.e., corticosteroids) may restore motor function. Food and water should be placed so that the animal can readily access it, urinary bladder expression may be required, frequent cleaning of the perineal area is required to prevent urine scalding and fecal soiling, and increased cage cleaning should be performed. If the vertebrae are fractured with displaced fragments or the spinal cord or nerves are severed or severely injured, recovery will not occur, and euthanasia should be considered.

References

Keeble E. Common neurological and musculoskeletal problems in rabbits. In Pract 2006, 28:212–218.

Owiny JR, VandeWoude S, Painter JT, et al. Hip dysplasia in rabbits: association with nest box flooring. Comp Med 2001, 51: 85–88.

Case 16

a. The tentative diagnosis is chronic renal failure (BUN, CREAT, urine S.G.). The condition is likely chronic because of the low PCV resulting from reduced erythropoietin expression.

b. Plans might include giving a balanced electrolyte solution IV immediately to correct the hydration status and then teaching the client to administer SC fluids subsequently. Potassium levels of the patient would have to be monitored and adjusted by supplementation in the fluids, as needed. The anemia could be treated by ferrous sulfate and B complex vitamins could be added. The animal may require oral gavage or nasogastric tube feeding of a high-quality food, such as an herbivore-specific critical care diet to treat anorexia. The urine should be cultured to determine whether a urinary tract infection is present, as this is common with chronic renal disease.

c. The treatment is palliative only and the owner should be counseled that the condition is chronic and degenerative. Quality of life may determine further treatment decisions.

Reference

Fisher PG. Exotic mammal renal disease: diagnosis and treatment. Vet Clin North Am Exot Anim Pract 2006, 9:69–96.



GUINEA PIGS

Case 17

a. This combination of clinical signs is typical for hyperthyroidism in guinea pigs.

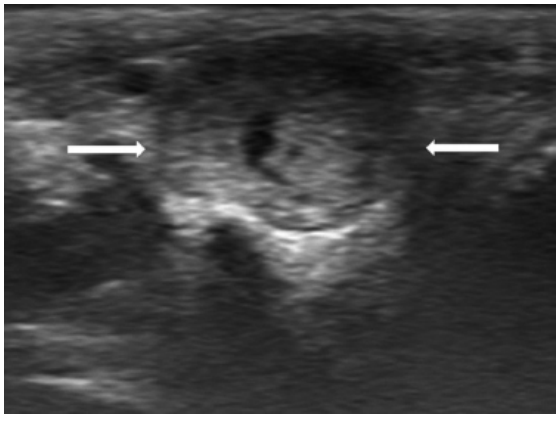


FIGURE 6.11. Ultrasound of the neck from a guinea pig displaying a partially cavitated thyroid mass (arrows) and hyperthyroidism.

b. Hyperthyroidism is commonly caused by a thyroid tumor in guinea pigs. On physical examination, a mass over the ventral neck is frequently palpated. In terms of diagnostic tests, a thyroid panel (free T4 and total T4) is recommended. Guinea pigs usually have a marked elevation in serum T4 levels, which is enough to confirm the diagnosis. An ultrasound of the mass can be performed to further characterize it (Figure 6.11). A fine-needle aspiration may be performed and submitted for cytology, but there is a risk of hemorrhage following the procedure. About half the thyroid tumors are malignant (thyroid adenocarcinoma) in guinea pigs. An echocardiographic examination also may be recommended as hyperthyroidism is associated with cardiac pathologies in some animals.

c. Most of these cases are treated medically with methimazole. Guinea pigs tend to require a higher dose than cats or dogs to achieve a reduction of total T4 within an acceptable range. Benign tumors tend to respond better than malignant neoplasms. Radioactive iodine (iodine 131) treatment is very effective in guinea pigs, but availability is a problem. Iodine therapy may be associated with better outcome because it targets neoplastic cells directly.

References

DiGeronimo PM, Brandão J. Updates on thyroid disease in rabbits and Guinea pigs. Vet Clin North Am Exot Anim Pract 2020, 23:373–381. 10.1016/j.cvex.2020.01.007.

Müller K, Müller E, Klein R, Brunnberg L. Serum thyroxine concentrations in clinically healthy pet guinea pigs (*Cavia porcellus*). Vet Clin Pathol 2009, 38:507–510. 10.1111/j.1939-165X.2009.00159.x.

Pignon C, Mayer J. Hyperthyroidism in a guinea pig (*Cavia Porcellus*). Pratique Médicale et Chirurgicale de l'Animal de Compagnie 2013, 48:15–20.

Case 18

a. There is a round, radiodense structure present in the pelvis, which is likely a urolith present at the neck of the bladder or in the urethra.
b. The cause of urolithiasis in guinea pigs is not known. Predisposing factors may include genetic predisposition, metabolic disorders, nutritional imbalances, inadequate water intake, and bacterial cystitis.
c. Treatment of choice is surgical removal after stabilization. Urethral calculi are more difficult to remove surgically. Catheterizing the urethra and back-flushing may retropulse the urolith into the bladder. Culture of the urine, stone, and bladder wall should be performed.
d. The prognosis is poor, as recurrence is common. Dietary manipulations are generally not successful, and urinary acidifiers are not indicated in guinea pigs as they have difficulty removing excess acid.

Reference

Fisher PG. Exotic mammal renal disease: diagnosis and treatment. Vet Clin North Am Exot Anim Pract 2006, 9:69–96.

Case 19

a. Tyzzer's disease, salmonellosis, coccidiosis, and cryptosporidiosis should be considered in cases involving chronic diarrhea in guinea pigs.
b. Cryptosporidial oocysts are 3–6 µm in diameter and are morphologically similar to yeasts. Diagnosis of cryptosporidial infection can be made from microscopic examination of concentrated fecal flotation samples or from acid-fast stains of fresh or formalin-fixed fecal smears or tissue sections.
c. *Cryptosporidium* spp. is highly infectious and may be transmitted by the fecal–oral route from various animal species to humans. It is a common cause of disease in immunodeficient humans.

Reference

Borel N, Ciuria S, Flury T, Basso WU, Ruetten M. Zoonotic potential of guinea pigs: outbreak of cryptosporidiosis combined with chlamydiosis in a breeding guinea pig herd. Schweiz Arch Tierheilkd 2023, 165:59–63. 10.17236/sat00383.

Case 20

a. This scenario is highly suggestive of bacterial infection exacerbated by stress. *Bordetella bronchiseptica* and *Streptococcus pneumoniae* should be considered and can be confirmed by culture. A likely scenario is that highly susceptible uninfected guinea pigs came in contact with asymptomatic carrier animals and that the stress associated with shipment resulted in the disease presentation.
b. The use of an autogenous bacterin or canine bacterium might have prevented a clinical outbreak of *Bordetella* infection, but this is not a common practice. Good husbandry, elimination of carriers, and stress reduction diminish the impact of streptococcal infections.
c. A broad-spectrum antimicrobial, such as enrofloxacin, should be administered to any animals that demonstrate respiratory signs or decreased activity or appetite. Parenteral vitamin C may help in treatment of sick animals and the diet should be evaluated to ensure appropriate levels of vitamin C are present. Nebulization can be considered for any animals that have respiratory involvement. Appropriate diet and husbandry and a low-stress environment should be provided, and these animals should be separated from other guinea pigs in the facility. Strains of *B. bronchiseptica* and *S. pneumoniae* can be carried by several species of animals, including rabbits, guinea pigs, cats, dogs, rats, and wild rodents, as well as humans.

Reference

Sparrow S. Diseases of pet rodents. J Small Anim Pract 2008, 21:1–16.

Case 21

a. If a multivitamin product was used in this guinea pig, other vitamins, especially vitamins D and A, may have been administered in excessive amounts.
b. Supplemental vitamin C should be provided whenever the vitamin C content of the feed is suspected to be inadequate. Excess vitamin C will be excreted in the urine as long as the animal is well hydrated and has functional kidneys. Many commercially available feeds for pets do not provide adequate levels of vitamin C and should routinely be supplemented. Heat, light, length of storage, diet composition, improper formulation, and dampness contribute to breakdown of the vitamin. Treatment dosages are between 25 mg/kg/day and 50 mg/kg/day for animals with clinical disease.
c. Guinea pigs, like humans, lack the enzyme L-gulonolactone oxidase, which is involved in the production of ascorbic acid from glucose.

Reference

Hickman DL, Wasson K, Ehrhart EJ. Morbidity and mortality in a group of young guinea pigs. Subclinical hypovitaminosis C Lab Anim 2003, 32:23–25.

Case 22

a. *Streptococcus equi* subsp. *zooepidemicus* is the probable etiologic agent. *Caviibacter abscessus* (previously *Streptobacillus moniliformis*) is another possible etiologic agent.
b. Dystocia, large fetal loads, salmonellosis, streptococcal infections, cytomegalovirus infections, miscellaneous infections, nutritional deficiencies, stress, and ketoacidosis may cause abortion or stillbirths in guinea pigs.

References

Bemis DA, Johnson BH, Bryant MJ, Jones RD, McCleery BV, Greenacre CB, Perreten V, Kania SA. Isolation and identification of *Caviibacter abscessus* from cervical abscesses in a series of pet guinea pigs (*Cavia porcellus*). J Vet Diagn Invest 2016, 28:763–769. 10.1177/1040638716665660.

Gruszynski K, Young A, Levine SJ, Garvin JP, Brown S, Turner L, et al. Streptococcus equi subsp. zooepidemicus infections associated with guinea pigs. Emerg Infect Dis 2015, 21:156–158. 10.3201/eid2101.140640.

Case 23

a. Salmonellosis in guinea pigs may cause generalized visceral congestion and focal necrosis of the spleen and liver.
b. Diarrhea may occur with *Salmonella* spp. infections, but this sign is an inconsistent finding. Affected animals may have a soft, discolored stool or may present with other nonspecific signs of illness.
c. Because of the epizootic and fatal consequences of a *Salmonella* spp. outbreak in a colony of animals, the persistence of the disease in a carrier state, and the public health significance, infected animals are generally euthanized.

Reference

Singh BR, Alam J, Hansda D. Alopecia induced by salmonellosis in guinea pigs. Vet Rec 2005, 156:516–518.

Case 24

a. Pododermatitis is common in obese guinea pigs housed on wire or abrasive floors. Poor sanitation is also a predisposing factor.
b. Inflammation can progress to osteoarthritis and systemic amyloidosis secondary to chronic staphylococcal infection.
c. Obesity management, wound cleaning/dressing and ulcer care, antimicrobials, and analgesia. Surgical treatment is often not successful because there is generally cellulitis and not an abscess to be removed. Incising the tissue typically causes a significant amount of bleeding.

Reference

Brown C, Donnelly TM. Treatment of pododermatitis in the guinea pig. Lab Anim 2008, 37:156–157.

Case 25

a. Mastitis in guinea pigs is commonly caused by *Streptococcus zooepidemicus* infections; however, other potential etiologic agents include staphylococcal, *Pasteurella* spp., and coliform organisms. Pups should be removed from the dam and sows should be treated with parenteral broad-spectrum antibiotics (e.g., fluoroquinolone antibiotics), analgesics, and hot packing of the affected glands. Affected animals may go off feed and become dehydrated. Sows should be tempted to eat with tasty food supplements and given access to fresh water.
b. Penicillin, and most other antibiotics, used in the guinea pig or hamster may induce an alteration of the intestinal flora that results in fatal enteritis or enterotoxemia.
c. Orphaned guinea pigs or those from dams with agalactia can be bottle-fed with kitten milk replacer diluted two or three to one with water. By 5–7 days, the young pups will begin to eat softened pelleted feed and can be weaned from milk by the third week. Guinea pig pups that are less than 55 g at birth rarely survive.

Reference

Kinkler RJ, Jr, et al. Bacterial mastitis in guinea pigs. Lab Anim Sci 1976, 26:214–217.

Case 26

a. Cytomegalovirus (CMV) infection produces eosinophilic intranuclear inclusions in submandibular salivary gland ductular epithelial cells. The ductal epithelial cells are markedly enlarged in infected guinea pigs. Smaller intranuclear inclusions may be found in renal tubular epithelial cells and occasionally in other tissues. Other potential infectious rule-outs for this clinical case include acute adenovirus infection or acute bacterial infection with a range of agents such as *B. bronchiseptica*, *Streptococcus* spp., *E. coli*, and *Salmonella* spp.
b. Cytomegalovirus infections are usually subclinical in guinea pigs. The prevalence of infection in conventionally housed and managed animals is usually high.
c. Although the guinea pig is an animal model for cytomegalovirus infections of humans, there is no evidence that the guinea pig virus can be transmitted between guinea pigs and humans. In fact, attempts to transmit guinea pig CMV to other species have failed.

References

Griffith BP, Hsiung GD. Cytomegalovirus infection in guinea pigs. IV. Maternal infection at different stages of gestation. J Infect Dis 1980, 141:787–793.

Griffith BP, et al. Enhancement of cytomegalovirus infection during pregnancy in guinea pigs. J Infect Dis 1983, 147:990–998.



CHINCHILLAS

Case 27

a. Indentation or collapse of the lateral mid-portion of the right bulla and lucency in the caudal portion of left mandibular body are visible (Figure 6.12).

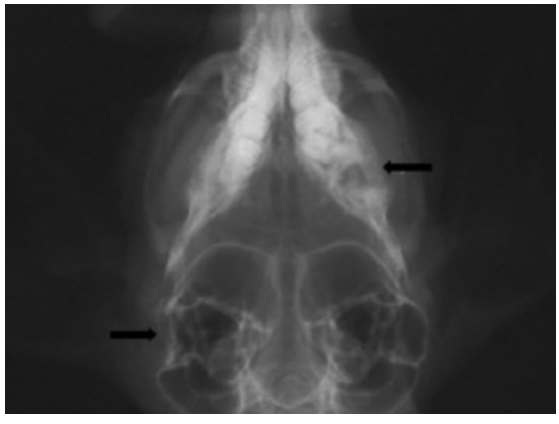


FIGURE 6.12. Ventrodorsal view of a chinchilla skull showing indentation of right bulla and lucency in left mandibular body (arrows).

b. Head tilt is due to damage to the vestibulocochlear nerve secondary to trauma, infection, inflammation, and neoplasia. Droopy right ear and lip is likely caused by damage to the facial nerve secondary to trauma, infection, inflammation, neoplasia. Indentation, or collapse of the lateral mid-portion of the right bulla was likely caused by fracture secondary to trauma. The bulla wall is very thin and chinchillas are very agile and enjoy running and jumping, and the animal may have, hit its head against the wall. Lucency in the caudal portion of the left mandibular body is interpreted as a chronic finding likely due to a tooth root abscess and possibly osteomyelitis of the surrounding bone.
c. Differential diagnoses for head tilt in a chinchilla include trauma, infections (otitis media/interna), parasites, neoplasia, central vestibular disease, and cerebrospinal nematodiasis.

Reference

Wideman WL. Pseudomonas aeruginosa otitis media and interna in a chinchilla ranch. Can Vet J 2006, 47:799–800.

Case 28

a. Dermatophytosis is most likely, as it is zoonotic and can be transmitted to people. In chinchillas, *Trichophyton mentagrophytes* is most commonly isolated, although *Microsporum canis* and *M. gypseum* may also occur.
b. Treatment options include topical or systemic antifungals, or a combination of both. Topical treatment removes spores from the hair shaft. Systemic treatment acts at the hair follicle. Topical treatment includes 2% chlorhexidine/2% miconazole shampoo, 0.2% enilconazole rinse, lime sulfur dips once weekly for 6 weeks, or orthocaptan fungal powder added to dust (one tsp. per two cups of dust). Note that orthocaptan may be carcinogenic and hands should be washed carefully after handling treated animals. Systemic treatment includes griseofulvin (25 mg/kg PO q24h × 30–60 d), ketoconazole (10–15 mg/kg PO q24h), itraconazole (5–10 mg/kg q24h), and terbinafine (8–20 mg/kg PO q24h).
c. The chinchilla likely acquired the infection from another chinchilla and may have been carrying the organism asymptomatically until now.

References

Mans C. Chinchillas. In: Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery, 4th ed. Quesenberry KE, Orcutt CJ, Mans C, Carpenter JW (eds.). St Louis, MO: Elsevier, 2021: 298–322.
Marshall KL. Fungal diseases in small mammals: therapeutic trends and zoonotic considerations. Vet Clin Exot Anim 2003, 6:415–427.

Case 29

a. It is important to know what type of antibiotics the chinchilla is being given. Inappropriate antibiotic use can result in intestinal dysbiosis, which favors overgrowth of *Clostridium* spp., elaboration of toxins, and fatal enterotoxemia. Antibiotics implicated in enterotoxemia of chinchillas include penicillins (including ampicillin and amoxicillin), cephalosporins, clindamycin, erythromycin, and lincomycin.
b. Treatment for antibiotic-associated enterotoxemia is supportive. The suspect antibiotic should be immediately discontinued. Provision of fluids warmed to body temperature is important to replace losses and maintain blood pressure. Intravenous or intraosseous administration is most helpful. Subcutaneous fluids may not be absorbed quickly enough to be effective. Analgesics are also indicated to minimize abdominal discomfort. Syringe-feeding a palatable, high-fiber diet will help prevent ileus and provide nutritional support. Pediatric simethicone may help reduce gas. The chinchilla should be kept warm but not overheated.
c. Antibiotic-associated enterotoxemia is a life-threatening condition and the prognosis is poor.

Reference

Donnelly TM, Brown CJ. Guinea pig and chinchilla care and husbandry. Vet Clin Exot Anim 2004, 7:351–373.

Case 30

a. Differentials include any bacteria that could result in septicemia, with *Listeria* spp. being the most likely, due to the epizootic nature of the infection. Toxoplasmosis may also cause abortions and pinpoint liver lesions.
b. *Listeria monocytogenes* may also cause sudden death, encephalitis with neurological signs, weight loss, depression, hunched appearance, droopy ears, diarrhea, or constipation with rectal prolapse, abdominal pain (stretching or rolling), bruxism, and vocalization.
c. The source is usually contamination of feed and/or water with rodent droppings.
d. Recommendations include improved sanitation of cages, water bottles and dust baths, minimizing stress, storage of food in rodent-proof containers, and purchasing food from reputable suppliers.

Reference

Sabocanec R, et al. Incidence of listeriosis in farm chinchillas (*Chinchilla laniger*) in Croatia. Veterinarski Arhiv 2000, 70:159–167.

Case 31

a. Heart murmurs are common in chinchillas. One study reported a 23% prevalence.
b. Differentials for this case are an "innocent" heart murmur and cardiac disease. Chinchillas with heart murmurs often have echocardiographic abnormalities, with valvular disease being the most common.
c. Echocardiography should be recommended for chinchillas with heart murmurs, especially older chinchillas with murmurs of grade 3 or higher. Thoracic radiographs may show an abnormal cardiac silhouette but may not be helpful for diagnosis. Electrocardiography may also be recommended if evidence of cardiac disease is found on echocardiography.
d. The owner should be advised to monitor the pet for weakness, reduced activity, reduced body weight, and/or appetite.

Reference

Pignon C, Sanchez-Migallon Guzman D, Sinclair K, Baey C, Pignon JP, Mayer J, Kittleson MD, Paul-Murphy J. Evaluation of heart murmurs in chinchillas (*Chinchilla lanigera*): 59 cases (1996–2009). J Am Vet Med Assoc 2012;241(10):1344–1347.



HAMSTERS

Case 32

a. Dermatophytosis, bite wounds from another hamster, cutaneous lymphoma, allergic or bacterial dermatopathies, and acariasis (*Demodex* spp) might cause lesions similar to those seen in this animal.
b. A thorough history should be performed to determine the type of bedding used and any other recent changes (weight or appetite loss, other hamster introductions in particular). A skin scraping, DTM culture, and possibly a biopsy or bacterial culture should be performed. Because this animal is owned by a child, it is important to rule out dermatophytes.
c. Prior to identification of the underlying cause, the area should be cleansed with an antibacterial/antifungal agent, such as chlorhexidine. Any husbandry-related recommendations (i.e., change bedding from cedar to hardwood, remove other hamsters that might be inflicting trauma) should be instituted. The cause of the problem should be determined, and an appropriate treatment used, such as ivermectin for demodicosis, systemic or local antifungals for dermatophytes, or systemic antibiotics for bacterial infections. Care should be exercised in administration of therapies with potential side effects.

Reference

Tani K, Iwanaga T, Sonoda K, et al. Ivermectin treatment of demodicosis in 56 hamsters. J Vet Med Sci 2001, 63:1245–1247.

Case 33

a. Pheochromocytomas, adrenocortical adenomas, and adenocarcinomas have been reported in golden hamsters and all may result in alopecia. They are relatively common among the neoplasms of hamsters. Cage trauma and demodicosis should also be considered. Neoplasia may predispose animals to demodicosis.
b. A scraping from the margin of the skin lesion should be examined for *Demodex* spp. and dermatophytes, although dermatophytosis is rare in the golden hamster. Alopecia in hamsters is also commonly associated with endocrinologic disease. Affected animals are generally over 14 months old, and while alopecia with or without comedones and hyperpigmentation may be the initial presenting sign, animals will develop polyuria, polydipsia, and skin fragility with time. There is no diagnostic test currently available for hamsters and diagnosis is usually a process of elimination. Similarly, there is no treatment other than supportive care for the condition.

Reference

Collins B. Endocrine diseases of rodents. Vet Clin Exot Anim 2008, 11:153–162.

Case 34

a. Histopathology with silver stains of the liver and ileum is recommended to rule out Tyzzer's disease (*C. piliforme*) and transmissible ileal hyperplasia ("wet tail") caused by *Lawsonia intracellularis*. In addition, a fecal evaluation should be performed for parasites, and fecal culture may also be indicated. It is important to consider that multiple etiologies may be involved and are likely related to husbandry factors, such as poor diet, inappropriate environmental conditions, transportation, and so forth.
b. Both transmissible ileal hyperplasia and Tyzzer's disease seem likely as they are common in pet store animals and present with symptoms similar to those described. Provision of appropriate husbandry is key to controlling further disease in the colony. Treatment includes supportive fluids (oral or parenteral electrolytes or lactated Ringer's solution) for dehydration, an antidiarrheal agent, such as bismuth subsalicylate, and appropriate antibiotics, such as tetracycline, enrofloxacin, metronidazole, or trimethoprim/sulfa, which can be administered orally or via the drinking water. Rats and mice in the facility may be carriers for Tyzzer's disease and should be housed in separate areas.
c. The prognosis is guarded for any animals that develop symptoms, as animals often do not respond to therapy.

References

Motzel SL, Gibson SV. Tyzzer's disease in hamsters and gerbils from a pet store supplier. J Am Vet Med Assoc 1990, 197:1176–1178.

Motzel SL, Riley LK. Subclinical infection and transmission of Tyzzer's disease in rats. Lab Anim Sci 1992, 42:439–443.

Shauer DB, et al. Proliferative enterocolitis associated with a dual infection with enteropathogenic Escherichia coli and *Lawsonia intracellularis* in rabbits. J Clin Microbiol 1998, 36:1700–1703.

Case 35

a. Renal disease with subsequent hypoproteinemia as well as cardiomyopathy with subsequent heart failure and poor peripheral circulation should be considered in these animals. A thorough history should also investigate other experimental factors that might have contributed to disease. A urinalysis could reveal urine-specific gravity and protein content, and an ultrasound might be performed to assess cardiac function if the appropriate transducers are available. Whole-body radiographs might also reveal cardiac or renal abnormalities. If the investigator decides to euthanize the animals, a necropsy should be performed. Diuretics can be initiated if this will not interfere with the experimental study.
b. Amyloidosis of the kidneys and other organs, cardiomyopathy, and renal disease are all common metabolic diseases of aged hamsters. Anasarca has been reported in cases of cardiomyopathy and amyloidosis.

References

Murphy JC, Fox JG, Neimi SM. Nephrotic syndrome associated with renal amyloidosis in a colony of Syrian hamsters. J Am Vet Med Assoc 1984, 185:1359–1362.

Ottenweller JE, Tapp WN, Natelson BH. The effect of chronic digitalis therapy on the course of heart failure and on endocrine function in cardiomyopathic hamsters. Res Commun Chem Pathol Phamarcol 1987, 58:413–416.

Case 36

a. Liver, kidneys, and gastrointestinal tract due to location of swelling. Due to the age of the animal and gradual onset, neoplasia is a top differential.
b. Polycystic disease most often affects the liver in hamsters.
c. The epididymis is the second most commonly affected organ in hamsters, followed by seminal vesicles and pancreas.

References

Percy DH, Barthold SW. Hamster. In: Pathology of Laboratory Rodents and Rabbits, 4th ed. Ames, IA: Wiley-Blackwell, 2016.

Powers CM, Akingbade GM, Phillips IL, Etzioni AL, Gilbreath E. Organomegaly, lethargy, and hind limb trembling in a 3-year-old intact male Syrian hamster (*Mesocricetus auratus*). J Am Vet Med Assoc 2022, 261:562–565.



GERBILS

Case 37

a. Cutaneous neoplasms have been associated with the ventral midline sebaceous scent gland in the gerbil. These neoplasms are usually benign but are occasionally malignant. In either case, resection of the mass is generally curative.
b. Torticollis indicates an inflammation of the inner ear or brain and may be secondary to otitis media/interna, a brain abscess or tumor, aural cholesteatoma, or trauma. If an inflammatory process damages the vestibular apparatus of the inner ear, the animal may never regain a normal posture. Administration of a steroid may reduce inflammation. If the torticollis is not severe, an affected animal may compensate and continue to eat and drink despite the head tilt. Alternately, head tilt can also result from pressure on the tympanic membrane due to the accumulation of keratin plugs produced by aural cholesteatomas in the external auditory canal.

References

Chole RA et al. Cholesteatoma: spontaneous occurrence in the Mongolian gerbil, Meriones unguiculatus. Am J Otol. 1981, 2: 204–210.

Henry KR et al. Age-related increase of spontaneous aural cholesteatoma in the Mongolian gerbil. Arch Otolaryngol. 1983, 109: 19–21.

Schiffer SP, Lukas VS, Chrisp CE. Diagnostic exercise: head tilt in a gerbil. Lab Anim Sci. 1986, 36: 176–177.

Case 38

a. Gerbils are weaned between 20 and 26 days of age. The gerbils in this case were sucklings.
b. Death in two animals just prior to weaning could be due to congenital defects that impaired prehension, such as malocclusion or hydrocephalus. No clinical signs were evident on necropsy that supported these diagnoses. Husbandry considerations would be related to temperature, particularly hyperthermia (unlikely because the mother and two littermates were unaffected), or inability to eat or drink. This would be possible if the animals could not reach or chew the food pellets, or if the sipper tube was inaccessible due to cage height. Stomach content and hydration status at necropsy could help to ascertain these parameters. In the case of this diagnosis, the other two littermates would presumably still be nursing or might be larger and therefore able to reach and procure food and water more effectively.

Reference

Donnelly TM. Disease problems of small rodents. Ferrets, Rabbits, and Rodents. 2004:299–315. 10.1016/B0-72-169377-6/50031-9.

Case 39

a. Rough hair coats in gerbils occur when the relative humidity is 50% or higher. Gerbils may also have rough hair coats if they are febrile, the water bottle leaks, or if the bedding is damp or contains resin. Gerbils can be provided with dust baths or bedding that is firmer and more abrasive than wood shavings (such as corncobs) to maintain high coat quality.
b. Gerbils are sexed by noting the anogenital distance, which in adults is about 5 mm for females and 10 mm for males. The female has a vulvar opening at the base of the urogenital papilla, whereas the male has a larger papilla. If the gerbils have identical arrangements of the anal and urogenital structures, they are not a male–female pair.
c. Gerbils should be provided with deep bedding and a concealed nesting and hiding place within the cage. Gerbils should be fed a quality, pelleted rodent feed from a hopper feeder and watered from a water bottle that is readily accessible. The water conservation mechanism of the gerbil is a mechanism for survival in the desert and should not be used as a rationale for excluding water from the pet or laboratory gerbil. Nesting boxes may be simple metal boxes, cans, or short pieces of plastic pipe or tubing.

Reference

Housing and husbandry: Gerbil. Available at www.nc3rs.org.uk/3rs-resources/housing-and-husbandry-gerbil (accessed March 1, 2024).

Case 40

a. Tyzzer's disease often involves focal hepatic necrosis, but other enteric conditions, including coliform infections, can pass via the portal circulation to the liver.
b. *Clostridium piliforme* is transmitted primarily through the ingestion of contaminated feces. Infectious, spore-like bodies from the filamentous organism may remain viable in the environment for months or years.
c. The classic triad of gross necropsy signs—myocarditis, hepatic necrosis, and typhlitis—together with Warthin–Starry visualization of bacilli in histologic sections, are commonly used methods for identifying the disease and the intracellular organism.

References

Motzel SL, Gibson SV. Tyzzer's disease in hamsters and gerbils from a pet store supplier. J Am Vet Med Assoc 1990, 197:1176–1178.

Veazey RS, Paulsen DB, Schaeffer DO. Encephalitis in gerbils due to naturally occurring infection with Bacillus piliformis (Tyzzer's disease). Lab Anim Sci 1992, 42:516–518.

Case 41

a. The cause of this is likely an increase in secretion of porphyrin material from the Harderian gland, which is irritating to the skin. Various skin bacteria, such as *Staphylococcus* spp., then act opportunistically to produce dermatitis.
b. The reddish-brown pigment is likely porphyrin from the Harderian gland. Stressors, such as those resulting from overcrowding or high humidity, are thought to increase secretion.
c. Keeping the gerbil in a dry environment, minimizing stress, and providing a sand bath may help prevent this condition. Antibiotic eye ointment can be used in the eye and on the skin. Parenteral antibiotics, such as chloramphenicol or trimethoprim/sulfa, are indicated in severe infections. Trauma to the nose from chewing at the bars of a wire cage or from a roughened cage surface may exacerbate the condition.

Reference

Mira Y, Mayer J. Hamsters and Gerbils. In: Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery, 4th ed. Quesenberry KE, Orcutt CJ, Mans C, Carpenter JW (eds.). St Louis, MO: Elsevier, 2021: 368–384.

Case 42

a. Differential diagnoses for this case are dystocia, hepatomegaly, reproductive tract disease, renal disease, primary respiratory disease, and metastatic lung disease.
b. Abdominal ultrasound should be performed to confirm the presence of ovarian cysts. Radiographs may rule out metastatic lung disease. Fine-needle aspiration may be performed with ultrasound guidance along with cytology of the aspirated fluid. Exploratory laparotomy may be needed to confirm the diagnosis. Ovarian cysts can be follicular, serous, or paraovarian. Histopathologic examination of surgically removed ovaries is necessary to rule out neoplasia. Ovarian tumors, mainly granulosa cell tumors, are the most common tumor of Mongolian gerbils.
c. Ovariohysterectomy is the treatment of choice for ovarian cystic disease. For ovarian neoplasms, ovariohysterectomy is the treatment of choice if there is no metastatic disease.

References

Malbrue RA, Arsuaga CB, Jay AN, Smith N, Dehghanpir SD, Kawabata A, et al. Pathology in practice. J Am Vet Med Assoc 2017, 250:989–992.

Norris ML, Adams CE. Incidence of cystic ovaries and reproductive performance in the Mongolian gerbil, *Meriones unguiculatus*., Lab Anim 1976, 6:337–342.

MICE

Case 43

a. Adult male mice housed in groups without adequate shelters or hiding places will often fight and bite one another. The fighting wounds, usually seen over the back, rump, and tailhead, include alopecia, scabbing, swelling, and ulceration. In some cases, abscessation occurs. The social

hierarchy existing within the group influences the relative severity of the lesions. This mouse had a staphylococcal abscess extending from beside the anus through the posterior abdomen and into the spinal cord and canal. Differential diagnoses include traumatic injury and neoplasia.

b. Adult male mice should be given appropriate cage resources to allow subordinate animals to escape unwanted attention from more dominant animals. Single housing should occur as a last resort.

References

Streiff C, Herrera A, Voelkl B, Palme R, Würbel H, Novak J. The impact of cage dividers on mouse aggression, dominance, and hormone levels. PLoS One 2024, 19:e0297358. 10.1371/journal.pone.0297358.

Weber EM, Zidar J, Ewaldsson B, Askevik K, Udén E, Svensk E, Törnqvist E. Aggression in group-housed male mice: a systematic review. Animals (Basel) 2022, 13:143. 10.3390/ani13010143.

Case 44

a. Mousepox should be suspected in all cases of epizootic mortality in a mouse colony, especially when that mortality is high and when the introduction of biological products or mouse tissues precedes the outbreak. Salmonellosis or other peracute bacterial infections could cause sudden deaths in susceptible strains of mice and should also be considered.

b. Recommendations should include PCR testing of the tissue for mouse pathogens or inoculation of the tissue into test mice maintained under strict quarantine (MAP test), use of sentinel mice within the experimental room, necropsy, and histopathology of tissues from affected animals, and repeated serologic testing.

c. Serologic testing, PCR testing, or virus inoculation of susceptible cell lines, mouse inoculation, and histopathologic examination are used to diagnose mousepox.

References

Lipman NS, Nguyen H, Perkins S. Mousepox: a threat to US mouse colonies. Lab Anim Sci 1999, 49:229.

Lipman NS, Perkins S, Nguyen H, et al. Mousepox resulting from use of ectromelia virus-contaminated, imported mouse serum. Comp Med 2000, 50:426–435.

Case 45

a. Pale viscera are indicative of anemia. As some of these mice had hemorrhagic enteritis, this may account for the anemia.

b. Inflammation of the intestinal wall, with edema and inflammatory cell infiltration, will result in a thickened intestinal wall, as will hyperplasia of the intestinal epithelium seen typically with *Citrobacter rodentium* or *L. intracellularis* infection. The rectum of mice is predisposed to prolapse with straining and hyperplastic colitis.

c. Enteric organisms that may be involved in colitis in mice include *Helicobacter* spp., *E. coli*, *C. rodentium*, *L. intracellularis*, *Salmonella* spp., MHV, and heavy pinworm infestations.

d. A complete necropsy with histopathology, serology, and culture for relevant organisms should be performed. Rooms with affected mice should be isolated; the affected mice should be quarantined and treated or euthanized pending diagnosis. The facility should be thoroughly disinfected and restocked, if feasible. Use of microisolator caging will reduce the transmission of the highly infectious disease agents.

Reference

Percy DH, Barthold SW. Mouse. In: Pathology of Laboratory Rodents and Rabbits, 4th ed. Ames, IA: Wiley-Blackwell, 2016.

Case 46

a. Diarrhea in infant mice may be caused by a wide variety of organisms, including rotavirus (epizootic diarrhea of infant mice [EDIM]), coronavirus (mouse hepatitis virus [MHV]), and reovirus 3. EDIM affects weanling mice under 21 days of age. Mortality remains low, and the feces may be pasty and yellow. Reovirus 3 infections are characterized by steatorrhea (oily diarrhea) in suckling mice. At necropsy, mice affected with reovirus 3 may have pale foci in the liver and other viscera. MHV, the most common of these three in research colonies, can result in high mortality, and the enteric form usually affects suckling animals. This case is most consistent with an outbreak of MHV. ELISA or indirect fluorescent antibody tests are serologic tests that may be used to establish a definitive diagnosis in exposed and recovered animals.

b. PCR can also be used to diagnose active infections.

c. Dermatophytoses, excessive grooming or barbering by cagemates, biting, urine–fecal irritation, and abrasion on a cage surface will cause focal alopecia in mice.

d. Many murine viruses may be shed asymptomatically in the feces. More commonly shed viruses include TMEV, MHV, rotavirus, MPV, and MMV.

e. Morbidity refers to the number of animals affected or infected. Mortality refers to the number of animals that die.

Reference

Rehg JE, Blackman MA, Toth LA. Persistent transmission of mouse hepatitis virus by transgenic mice. Comp Med 2001, 51:369–374

Case 47

a. The most likely diagnosis for this syndrome, given the widespread nature of the condition and pruritus, is lice or mite infestation.

b. If the condition were confined to scabs and wounds in males, the likely diagnosis would be fighting. If females had areas of alopecia with no dermatitis, and were lacking whiskers, then barbering should be considered.

c. Skin scrape and DTM culture should be performed. Instead of performing a deep follicular scrape, which could cause significant trauma to the mouse, particularly if the wounds are around the eyes, shafts of hair around the affected lesions could be plucked and examined under mineral oil. DTM cultures are similar to those performed in dogs and cats. If one animal can be euthanized, histopathology and examination of the pelage for mites can be performed. Response to therapeutic trials with antiparasitics can also be used to assess infestation.
d. A variety of agents can be used to treat mouse lice. These include ivermectins, pyrethrins, and organophosphates. Ivermectins are highly effective and have a high therapeutic index, though some rare strains lack a complete blood–brain barrier and can suffer neurotoxicity following exposure to ivermectin and its derivatives. Environmental decontamination should also be performed simultaneously. While feeding a snake a mouse that has recently been treated with ivermectin should be avoided, the drug is not toxic to reptiles.

Reference

Merck Manual. Diseases and Disorders of Mice. Available at https://www.merckvetmanual.com/all-other-pets/mice/diseases-and-disorders-of-mice (accessed March 2, 2024).



RATS

Case 48

a. An adult male rat typically weighs 450–520 g; this rat is in poor body condition.
b. The red discharge is likely chromodacryorrhea, or excessive porphyrin excretion in tears that is associated with stress.
c. Direct smear, gross and microscopic signs, culture, and serologic testing will provide a diagnosis.
d. Bacteria associated with pneumonia in rats include *Mycoplasma pulmonis*, *Filobacter rodentium*, *S. pneumoniae*, *Corynebacterium kutscheri,* and *Rodentibacter heylii*. *M. pulmonis* is a very common respiratory pathogen in rats that results in chronic pneumonia presenting as dyspnea in older rats. *Filobacter* and coronaviruses may also contribute to chronic respiratory disease of rats. Therapy for chronic respiratory disease includes provision of oxygen supplementation, if dyspnea is severe, and broad-spectrum antibiotics administered parenterally or via nebulization. Note that antibiotic therapy is palliative and not curative in chronic respiratory disease. Feeding moistened high-quality food will help support nutritional needs and hydration. The long-term prognosis is poor.
e. Older male rats are also predisposed to neoplasia, including testicular tumors (interstitial cell or Leydig tumors), chronic renal disease, and myocardial degeneration.

Reference

Percy DH, Barthold SW. Rat. In: Pathology of Laboratory Rodents and Rabbits, 4th ed. Ames, IA: Wiley-Blackwell, 2016.

Case 49

a. Subcutaneous masses in rats are usually mammary neoplasms, although abscesses and fibrosarcomas should also be considered.
b. Mammary neoplasms in rats are most often benign fibroadenomas, although adenocarcinomas may also occur.
c. Surgical removal under general anesthetic is an appropriate treatment as masses are typically benign.
d. The masses are unlikely to reoccur following surgical excision, but other mammary tumors may grow from other sites. It is impractical to ablate all the mammary tissue in the rat as it is extensive. Concurrent spay may reduce the incidence of tumor growth; however, prolactin-secreting pituitary adenomas may also induce mammary tumor growth in rats.

Reference

Hotchkiss CE. Effect of surgical removal of subcutaneous tumors on survival of rats. J Am Vet Med Assoc 1995, 206:1575–1579.

Case 50

a. Long–Evans rats have dark hair over the head and dorsoanterior trunk and are often described as "hooded" rats.
b. The causative agent of sialodacryoadenitis in rats is a coronavirus. It could be definitively diagnosed by culture or PCR during active infection or serologic analysis after recovery.
c. Corneal damage would result from the decreased or absent lacrimal secretion and from trauma resulting from scratching the irritated area with the feet (self-traumatization).
d. Use of microisolator caging can slow the spread of disease, which is highly contagious. Strict hygiene including changing all clothing and autoclaving and complete sanitization of all bedding, cages, and implements that could serve as fomites should be instituted to prevent further spread of the disease.

Reference

Hajjar AM, DiGiacomo RF, Carpenter JK, et al. Chronic sialodacryoadenitis virus (SDAV) infection in athymic rats. Lab Anim Sci 1991, 41:22–25.

Case 51

a. Judging by the location of the lesions on lesser-haired parts of the body, the lesions were probably thermal burns caused by heat from the heating pad. Heat lamps or hot water bottles may cause similar burns.

b. Anesthetized animals are susceptible to burns from hair dryers, heat lamps, or heating pads because animals cannot move away from the heat source and anesthesia suspends reflex vasoconstriction in response to heat. A circulating water blanket with a calibrated temperature setting should always be used in lieu of a heating pad.

Reference

Bailey KT, Jantre SR, Lawrence FR, Hankenson FC, Del Valle JM. Evaluation of active warming and surgical draping for perioperative thermal support in laboratory mice. J Am Assoc Lab Anim Sci 2022, 61:482–494. 10.30802/AALAS-JAALAS-21-000036.

Case 52

a. Findings are consistent with *Trichosomoides crassicauda* infection.
b. Examine urine for parasite ova by collecting urine (use of metabolism cages and 2% glucose in 0.09% saline for drinking water to cause diuresis), followed by filtration. Use a syringe to force the urine through a 22-mm diameter, coarse Millipore prefilter, which retains the eggs and examine the filter microscopically at 40×. The dark, brownish-yellow, bioperculate eggs are seen readily. Histologically, one may see profiles of adult parasites and eggs in the walls of the urinary bladder, ureter, or pelvis of the kidney, as well as migrating larval forms in the lungs.
c. Administration of a single 200 µg/kg SC dose of ivermectin and institution of an effective cage cleaning routine associated with repeated transfer of recently treated animals to clean cages represents an appropriate course of action. This will eliminate cages as fomites for transmission of eggs.
d. Adult female worms live partially embedded in the mucosa of the urinary tract and pass eggs intermittently in the urine. The small males reside inside the reproductive tract of female worms. Eggs ingested by a rat hatch in the stomach, and the resulting larvae migrate, via the lungs, to the kidneys and urinary bladder, where the worms mature.

Reference

Findon G, Miller TE. Treatment of *Trichosomoides crassicauda* in laboratory rats using ivermectin. Lab Anim Sci 1987, 37:496–499.

INDEX

A
Abandonment, gerbils, 79
  hamsters, 72
  mice, 236
Abortion
  See Prenatal mortality
Abscesses
  antibiotic-impregnated beads and, 178
  C. kutscheri, 269
  chinchillas, 220
  gerbils, 228
  guinea pigs, 181–182, 211
  hamsters, 66, 222
  mice, 84, 231
  P. multocida, 329
  Rodentibacter complex, 340
  pododermatitis, 364
  rabbits, 138, 178, 200, 255
  rats, 238
  S. aureus, 348
  S. zooepidemicus, 351
Acariasis (mite infestations), 245–2
  clinical signs
    guinea pigs, 249
    hamsters, 250
    mice, 251
    rabbits, 247
    rats, 253
  diagnosis, 246
    guinea pigs, 249
    hamsters, 250
    mice, 251
    rabbits, 248
    rats, 253
  gerbils, 251
  guinea pigs, 249–250
  hamsters, 250–251
  hosts, 245
  mice, 251–253
  predisposing factors, 245
  prevention, 247
    rabbits, 249
  public health significance
    guinea pigs, 250
    hamsters, 250
    mice, 252
    rabbits, 249
    rats, 253
  rabbits, 247–249
  rats, 253–254
  transmission, 245
    mice, 251
    rabbits, 248
    rats, 253
  treatment, 246
    guinea pigs, 250
    hamsters, 250
    mice, 252
    rabbits, 248
    rats, 253
Acepromazine maleate, 148
  dosages/uses for, rabbits, 158, 150t, 160
Acute enzootic pneumonia, 329
Acyclovir, 316
Adenocarcinoma, uterine
  hamsters, 225
  rabbits, 116, 132, 294, 318
Adenoviruses
  diagnostic serology tests for
    guinea pigs, 214
Adrenal gland tumors, in hamsters, 229, 319
Aflatoxicosis, rabbits, 119
Aggression
    male rabbits, 25, *26*, 30
  hamster, 68
  mice, 84, *84*
AIDS and *Cryptosporidium* spp, 271
Allergies
  of mice to fur mites, 232
  of rabbits, 204
  to rabbits and rodents, 16–17, *16*, 56, 91, 102
Allometric scaling, 142
Alopecia
  gerbils, 228 228t
  guinea pigs (and chinchillas), 211, 212t, 220
  hamsters, 222, 222t, 225
  mice, 230, 231t
  rabbits, 200, 201t
  rats, 237, 237t
Alpha-2-agonist induced myocardial necrosis, rabbits, 204
American Type Culture Collection strain 12960
  S. zooepidemicus, 352
Amikacin
  dosages, 142, 143t, 145t
Aminoglycosides
  as cause of ascending flaccid paralysis, 142
Amitraz (MAO inhibitor) dosages, 143t. 146t, 228
Ammonia gas
  as disinfectant, 16
  as predisposing factor to infections, 12, 311
Ampicillin
  dosages, 143t, 145t
Amprolium 9.6% (oral solution), dosages, 143t
Amputation of limbs
  in mousepox, 308
Amyloidosis, 126
  gerbils, 225
  guinea pigs, 214t
  hamsters, 223, 224t, 227t
  mice, 232, 233t, 234, 235t
  with nephrosis, 323
Analgesia
  general information, 147, 169–174, 171t, 172t
  nonsteroidal antiinflammatory drugs (NSAIDs), 172
  opiates and opioids, 170
  pain ladder, 170
  suggested dosages, 171t, 172t
Anemia, 116, 118, 120, 122, 142
  hamsters, 226t
  mice, 232, 320, 332
  rabbits, 200, 206t, 331
  rats, 253, 322
Anesthesia, 147
  administration of, 148
  cardiopulmonary resuscitation, 151
  chinchilla, 162–163, *163*
  endotracheal intubation general information, 149, 158,
    rabbits, 152, *158*
    rodents, 164, 164, 166
  epidural, rabbits, 154
  fluids, intraoperative, 153
  gerbils, 164
    inhalant, 164
    injectable, 164
  general information, 147–148
  guinea pigs, 161–162
    endotracheal intubation, 161
    inhalant, 161
    injectable, 162
  hamsters, 163–164
    inhalant, 163
    injectable, 163–164
  Hypnorm (fentanyl/fluanisone), dosages/uses for, 161
  injection procedures, 152, *152*
  laryngeal mask airway, 152, 159, *159*

Harkness and Wagner's: Biology and Medicine of Rabbits and Rodents, Sixth Edition. Patricia V. Turner, Colette L. Wheler, Hugues Beaufrère, Niora Fabian, and John E. Harkness.

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Anesthesia *(Continued)*
mice
endotracheal intubation, 164, *164*
inhalant, 164
injectable, 164–165
monitoring, intraoperative, 149, *149,* 153
nonrebreathing anesthetic circuit, 158
other
alphaxalone, 159
fentanyl/fluanisone (Hypnorm), 161
tribromoethanol, 165
overdose, 153
perioperative care, 149, 153
perioperative fluids, 153, *154, 155, 156*
preanesthetic drug dosages, 150t
preoperative procedures, 147
preoxygenation, 147
respirator settings, 162, 166
respiratory failure, treatment of, 153
rabbits, 157
atropine, responses to, 157
continuous rate infusion protocols, 160t
endotracheal intubation, 158, *158*
induction, face mask, 158, *158*
inhalant, 157
injectable
general information, 159
ketamine combinations, 159–161
propofol, 161
Hypnorm, 161
laryngeal mask airway, 159, *159*
monitoring depth, 158
nonrebreathing circuit, 158
preanesthetic considerations, 157
rats, 165–166
endotracheal intubation, 166
inhalant, 166
injectable, 166
sudden death and, 147, 148
topical, 157
Aneurysms, uterine venous, rabbits, 208, 209t, 294
Animal numbers
as food and fiber species, 1
as pets, 1
in research, 1
Animal Welfare Act, 4
Anorectal papilloma, 203
Anorexia, 254–266
and reduced food intake
clinical signs, 254, 290
diagnosis, 264
etiology, 254
treatment, 254
hamsters, 223, 224t, 225
guinea pigs (and chinchillas), 211–212, 214t, 220, 299
malocclusion as a cause of, 306
mice, 232, 233t
rabbits, 203t, 209, 287
See Weight loss
Antifungal agents, 143t, 145t
Antiinflammatory drugs, *See* NSAIDs
Antimicrobials
and development of enterotoxemia, 279
and dysbiosis, 279
dosages
hamsters, gerbils, rats, mice, 145t
rabbits, guinea pigs, chinchillas, 143t
general comments, 142
toxic/lethal effects of, chinchillas, hamsters, gerbils, guinea pigs, rabbits, 142
Antibiotic-impregnated beads
for rabbit abscess, 178, 179
for rabbit enucleation, 138
for rodent abscess, 181
Antiparasitic agents
dosages
hamsters, gerbils, rats, mice, 145
rabbits, guinea pigs, chinchillas, 143
Antipyretic drugs. *See* NSAIDs
Apodemus sylvaticus, 288, 303
Appendage amputation, mice, 308
Arenavirus (RNA; LCMV), 304
Arthritis
zoonotic, *Pasteurella*, 331
Artificial insemination, rabbits, 37, 39, *39*
Ascorbic acid
administration of, 187
guinea pig requirements, 51, 52, 55
treatment of hypovitaminosis C, guinea pigs, 258, 298–300
Aspartate aminotransferase (AST), *See* Clinical chemistry, species
Aspergillosis, rats, 239t
Aspergillus, 63, 239
Aspiculuris tetraptera, 324–326
Astrovirus infections, 256
Ataxia, 229, 240, 327
Athymic
mice, 266
rats with SDAV, 266, 268
Atropine sulfate, 148
Atipamezole, dosages/uses for, 150t, 151t, 153, 160, 163, 164, 165, 166
Audiogenic seizures, mice, 91, 234, 241t
Auricular chondritis, 237, 239
Autoimmune nephrosis, 323
Avocado leaf ingestion, 204
Azithromycin, 142, 143t, 178, 184

B

Bacitracin
uses, 278
Bacterial dermatopathies, 200
Bacterins, 258, 352
Barbering
gerbils, 228
guinea pigs, 212t
mice, 84, *84*, 230, 231t
rabbits, 200, 201t
rats, 237, 237t
Barr bodies, guinea pigs, 122
Baylisascaris spp., 205, 206t, 207, 220
Bedding
for chinchillas, 58, 139
for guinea pigs, 48, 50
for gerbils, 77, 78, 228t, 229
for hamsters, 67, 69, 70, 72, 225
for mice, 85, 87, 90, 233, 234
for rats, 98, 99, 101, 237, 237t, 239
general, 7, 9t, 11, 12, 17
pododermatitis and, 334–335
volatile oils and, 147
Beetles, 259
Behavior (also see individual species), 3–4
Behavioral management, *7,* 8, 10
Benzathine penicillin, 143t, 350
Biodata, see individual species
Bismuth subcitrate, 293
Bismuth subsalicylate, 278, 302
Black rat, 290
Blepharitis
guinea pigs, 138
mice, 304
rabbits, 137, 207
Blepharospasm, 135, 178, 240
Blood collection
adult blood volumes, 105, 105t, 117t, 123t, 125t, 126t, 127t, 128t
chinchillas, 110
general information, 9t, 104–105
guinea pigs, 109–110, *109*,
hamsters and gerbils, 110, *110*
rabbits, 105t, 106–107, 106t, *107*,
saline perfusion, 115
rats and mice, 110–113, *111, 112, 113*
rodents, 107–113, 108t
terminal, 113
Blood pressure monitoring, rabbit, 10t, 153, *154*, 174
Bloody or pigmented urine. *See* Hematuria, rabbits, 208, 294–295
Blow flies, 315
“Blue breast”, 307
“Blue fur disease”, 356
Body condition scoring, 38, *38*, 88, *89*, 254
Bone marrow collection, 114
Bordetella bacterin, dosages/uses for, 258
Bordetella bronchiseptica infections, 256–258
chinchillas, 220
*c*linical signs, 257
diagnosis, 257
etiology, 257
guinea pigs, 138
hamsters, 224
hosts, 256
necropsy signs, 257
predisposing factors, 257
prevention, 258

public health significance, 258
rabbits, 205t
transmission, 257
treatment, 257–258
Bordetella hinzii, mice, 256
Bot-flies, *See* Myiasis
Brown fat
rabbits, 41
rodents, 94
Brown rat. *See* Rats
Bruce effect, 90
Brucella spp, 208, 209t
"Buck teeth", 305 *See also* Malocclusion
"Bumblefoot," 211, 234 *See also* Pododermatitis
Buphthalmia, rabbits, 37, 207, *208*
Buprenorphine, *See* Analgesia
Butorphanol tartrate, *See* Analgesia
B-vitamins, 46, 255

C

C57BL/6 mice, *83, 84*, 84
Cages
cleaning and disinfection of, *See* Housing
"Caked udder", 307
Calcium, excess dietary, 294
Calicivirus, 204, 205t, 337
Calliphorid flies, 315
Canadian Council on Animal Care, 1, 4, 11t, 31t, 69, 85, 97, 102
Cannibalism
gerbils, 78, 230
hamsters, 72, 226
mice, 91
rabbits, 41, 208
rats, 101
CAR bacillus infections, *see Filobacter* Rodentium infections
Carbamate 5%, dosages/uses for, 146t
Carbohydrates, fermentable, requirements
rabbits, 33, 34, 35
Carbon dioxide
chemical changes caused by, 194
for euthanasia, 193, 194
Carbon monoxide, used for euthanasia, 193, 194
Cardiac puncture, 104, 106, 106t, 108t, 110, 113, 122, 123
Cardilipin antigen, 360
Cardiomyopathy
chinchillas, 220
general, 290
hamsters, 68t, 224, 225t, 226
guinea pigs,
mice, 226t
rabbits, 204, 264
Castration. *See* Orchidectomy
Casts
urinary, 128, 323
traction, 183
Cataracts
chinchillas, 139, 220
hamsters, Chinese, secondary to diabetes mellitus, 139
gerbil, *139*
guinea pigs, 139, 217
mice, 140, 234
rabbits, 136, 137, 138, 207
rats, 98
Catheters
endotracheal tubes from, 152, 166
general, 9t, 110, 112
intravenous, 148
rabbit, 153, 154
Cavia aperea, 45
Cavia porcellus, 45
CDT-producing *E. coli*, 281
Cellophane tape test, *191*, 192, 246, *246*, 252, 253, 325, 332
Cedar bedding and volatile oils, 70, 85, 147
Cephalosporins, as cause of enterotoxemia, 142, 258, 277, 279
Cerebellar hypoplasia, parvovirus, 327
Cerebral spinal fluid collection, rabbit, 114–115
Cervical dislocation, euthanasia by, 193, 194
Cervical lymphadenitis, guinea pigs, 212t, 351
Cestodiasis (tapeworm infestations),
clinical signs, 259
diagnosis, 259–260
etiology, 258–259
hosts, 258
necropsy signs, 259
predisposing factors, 2259
prevention, 260
public health significance, 268
transmission, 259
treatment, 260
Cheek pouches, in hamsters, 65, 66, 67, *67*, 72, 222, 222t, 223
"Cherry eye," rabbits, 136, 207. *See* prolapsed gland of third eyelid, rabbit.
Cheyletiella parasitivorax, 200, 201t, 245, 247, 248, 249, *249*
Chinchilla
anatomic and physiologic characteristics, 57–58,
dental anatomy, 57–58, *58*
dental formula, 57
reproductive anatomy, 61–62, *62*
as companion animals, 58–59
behavior, 58
life span, 58
restraint, 58–59, *59*
biodata, 63, 64t
disease prevention, 63
dust bath, 59–60
feeding and watering, 61
hand rearing, 63
housing, 59–60, *60, 61*
husbandry, 8–11
identification, 14–15
origin and description, 57
public health concerns, 63
reproduction, 61
breeding programs, 62
estrous cycle, 62
neonatal life, 63, *63*
palpating for pregnancy, 63
sexing and anatomy, 62, *62*
research, uses in, 63
temperature and humidity guidelines, 59
used for fur, 1
Chinchilla chinchilla, 57
Chinchilla lanigera, 57
Chinese hamster, 66
Chirodiscoides caviae, 211, 212t, 249
Chlamydiosis, 217
Chlamydophila spp., 136, 207
and guinea pig conjunctivitis, 138
Chloramphenicol
dosages, 142, 143t, 145t, 282, 317, 350, 351, 358
Cholangiohepatitis, with *Helicobacter*, 292, 293
Cholesteatomas, in gerbils, 228, 228t
Cholestyramine, dosages/uses for, 144t, 278, 280
Chromodacryorrhea
gerbils, 229, 317
as manifestation of pain, 95, 170
rats, 94, 140, 239, 240, *240*, 268
Chronic nephrosis. *See* Nephrosis
Chronic renal disease. *See* Nephrosis
Chylothorax
rabbits, 204, 205t
rats, 239t, 240
Ciliary body, rabbits, 136, 1376
mineralization, 217
Ciprofloxacin
dosages, 143t, 145t, 330, 351
Circling, guinea pigs, 49, 216
Citrobacter spp., 352
Citrobacter freundii 4280, 352
Citrobacter rodentium, 91, 229, 233t, 352–353
Clethrionomys spp., 288
Clindamycin, as cause of enterotoxemia, 142, 258, 277, 279
Clinical chemistry
chinchillas
clinical chemistry, 124t
hematology, 124t
physiologic values, 124t
general discussion, 122
gerbils
clinical chemistry, 126t
hematology, 126t
physiologic values, 126t
guinea pigs

Clinical chemistry *(Continued)*
clinical chemistry, 123t
hematology, 123t,
Barr bodies, 122
Kurloff cells, 124
physiologic values, 123t
hamsters
clinical chemistry, 125t
hematology, 125t
physiologic values, 125t
mice
clinical chemistry, 127t
hematology, 127t
Howell-Jolly bodies, 122
physiologic values, 127t
rabbits
clinical chemistry, 116–122
hematology, 116–118, 117t
physiologic values, 117t
urinalysis, 121–122
rats
clinical chemistry, 128t
hematology, 128t
Howell-Jolly bodies, 122
physiologic values, 128t
small rodents
clinical chemistry, 125–126
hematology, 122–124
urinalysis, rodents, 127–128
Clostridial enterotoxemia, 279–281
clinical signs, 280
diagnosis, 280
etiology, 279
hosts, 279
necropsy signs, 280
predisposing factors, 280
prevention, 280–281
public health significance, 281
transmission, 279
treatment, 280
Clostridium difficile, 47, 202, 203t, 213, 214t, 224t, 258, 277, 279, 280, 281, 292
Clostridium perfringens, 213, 224t, 229, 280, 281
Clostridium piliforme, 91, 188t, 202, 203t, 353, 354–356
Clostridium sordellii, 279
Clostridium spiroforme, 202, 203t, 279, 280, 281
Coccidiosis
hepatic, 260–263
clinical signs, 261
diagnosis, 261, *261*
etiology, 261
hosts, 260–261
necropsy, 273
predisposing factors, 261
prevention, 262
public health significance, 262
transmission, 261
treatment, 262
intestinal, 263–264
clinical signs, 263
diagnosis, 263
etiology, 263
hosts, 263
necropsy, 264
treatment, 264
Coccidiostats, used in rabbits, 264t
Cockroaches, 259, 343
Coenurus serialis, 138, 139, 200, 207, 220, 259
Colibacillosis, 281–283
clinical signs, 282
diagnosis, 282, *282*
etiology, 281
hosts, 281
necropsy signs, 282
predisposing factors, 282
prevention, 282
public health significance, 282–283
rabbits, 202, 283
transmission, 281
treatment, 282
Colonic hyperplasia, mice, 352–353
Conjunctival pseudopterygium, 136, 138, 178, 207
Conjunctivitis, 358
chinchillas, 220
gerbils, 228, 229, 233
guinea pigs, 217, *298*
hamsters, 225
mice, 234, 340, *341*
rabbits, 207, 297, 330
rats, 240, 268
Constipation
guinea pigs (and chinchillas), 213, 214t
hamsters, 223–224, 224t
mice, 233t
rabbits, 63, 202, 203t, 204, 283, 284
Contrast radiography, 133, 287
Convulsions, *See* Seizures
Copper sulfate, 278
Coprophagy
hamsters, 71
rabbits, 33, *33*, 34, 36
Corneal dystrophy
mice, 234
rabbits, 137, 207
rats, 240
Corneal hypoxia
rats, 140, *140*, 240
Corneal opacities, 134, 136, 137, 140
Corneal ulceration
rabbits, 137, 207
rats, 140
Coronavirus infections, 264–269
guinea pigs, 254
mice, 265–267
clinical signs, 265
diagnosis, 266, *266*
etiology, 265
necropsy signs, 266
predisposing factors, 265
prevention, 266–267
public health significance, 267
transmission, 265
treatment, 266
rabbits, 264
rats, 267–269
clinical signs, 268
diagnosis, 268
etiology, 267
necropsy signs, 268
predisposing factors, 267–268
prevention, 268
public health significance, 269
transmission, 267
treatment, 268
Corynebacteriosis. *See Corynebacterium kutscheri* Infections
Corynebacterium kutscheri infections, 269–270
clinical signs, 269
diagnosis, 270
etiology, 269
hosts, 269
mice, 253
necropsy signs, 269
predisposing factors, 269
prevention, 270
public health significance, 270
rats, 239t
transmission, 269
treatment, 270
Cricetidae family. *See* Hamsters; Rats
Cricetulus griseus (Chinese hamster), 66
Cricetulus mirgratorius (Armenian hamster), 66
Cricetulus cricetus (European hamster), 66
Cryptosporidiosis, 270–272
clinical signs, 271
diagnosis, 2271
etiology, 270
guinea pigs, 212
hosts, 270
necropsy signs, 271
predisposing factors, 271
prevention, 271
public health significance, 271
rabbits, 199
transmission, 270–271
treatment, 271
Cryptosporidium spp., 202, 276, 280,
CT scans, 10t, 130, *131*, *132*, 274, 287, 306
Ctenocephalides felis/canis, 200, 212t
Cutaneous conditions, clinical signs and differential diagnoses

chinchillas, 220
gerbils, 228–229, 228t
guinea pigs and chinchillas, 212t
hamsters, 222–223, 222t
mice, 230–232, 231t
rabbits, 200–201, 201t
rats, 237–239, 237t
Cutaneous hemangiosarcoma, hamsters, 320
Cutaneous lymphoma, hamsters, 320
Cuterebra spp., 200, 201t, 313–314
Cuterebriasis. *See* Myiasis
Cyclocryotherapy, 137
Cyclopia, rabbits, 138, 207
Cysticercus fasciolaris, 259
Cysticercus pisiformis, 259
Cystic ovaries
gerbils, 228, 228t, 320
guinea pigs, 211, 212t, 217, 2185
Cystitis (urinary bladder)
guinea pigs, 269, 323, 353
rabbits, 294, 295
Cystocentesis
rabbits, 113, *113*
rodents, 114
Cystotomy
rabbits, 176
rodents, 182, *182*
Cysts
biliary, 225
ovarian, *See* Cystic ovaries
renal, 209t
Cytomegaloviruses
guinea pigs, 214, 215t
hamsters, 225

D

Dacryoadenitis
gerbils, 229
rats, 240
Dacryocystitis
rabbits, 135, 136, 137, 184, 207, 305
DDT poisoning, 208
Death, sudden
anesthesia, 148
chinchillas, 221
gerbils, 230
guinea pigs, 217
hamsters, 226
mice, 236
rabbits, 204, 210
rats, 241
Decapitation, euthanasia by, 193, 194
Demodecosis
gerbils, 251
hamsters, 250
Demodex aurati, 250
Demodex criceti, 250
Demodex cuniculi, 200, 201t, 248
Demodex, hamsters 250
Dental disease, 254, *133*, 135, 305–307
hamsters, 67, *67*
guinea pigs, 51
rabbits, 34, *131*, 136, 137, 138, 178, 287
Dental formulas, 186t
Dental procedures, 183–185, *185*
cheek tooth removal, rabbit, 185
equipment, 306
incisor trimming, 184
incisor removal, rabbits, 184–185
too trimming, 8, 184
Dentostomella translucida, 229
Dermanyssus spp., 251
Dermatitis
chinchillas
gerbils, 139, 228–229, 228t, *229*, 317
guinea pigs, 211, 212t, *213*, 306
hamsters, 222t, 223
mice, 231t, 232, *232*, 251, 252, 356–357, *357*
rabbits, 137, 200–201, 201t 297, 305
rats, 237, 237t, 238–239, 253, 348
Dermatophytosis (ringworm), 272–273
chinchillas, 59, 212t, 220, *272*
clinical signs, 272
diagnosis, 272
etiology, 272
guinea pigs, 138, 212t
hamsters, 222, 222t
hosts, 272
mice, 231, 231t, 232
predisposing factors, 272
prevention, 273
public health significance, 273
rabbits, 43, 201, 201t
rats, 237, 237t
transmission, 272
treatment, 273
Diabetes mellitus
chinchillas, 220
Chinese hamsters, 66, 139
gerbils, 229
guinea pigs, 127, 215, 217
hamsters, 225
mice, 233
guinea pigs, 130, 358
rabbits, 120, 122, 205
rats, 2420Diagnostic serology tests, 184–186
Diaphragmatic hernia
gerbils, 229
guinea pigs, 215
Diarrhea
gerbils, 229
guinea pigs, 212–213, 214t, 298
hamsters, 223, 224t, 301
mice, 232, 233t, 342
rabbits, 202, 203t, 256, 261, 263, 264, 276, 277, *277*, 279–283
rats, 239, 342
Diazepam
dosages/uses for, rabbits, 158, 159
Dichlorvos, 235
Dihydrostreptomycin
fatal reaction to, 142
Disease
facility cleaning, disinfection, and fumigation, 15–16
Disinfectants, 15–16, 32, 262
Disinfection, 15–16
Disseminated intravascular coagulation (DIC), 208, 294
Djungarian hamster, 65
Dobrava virus, 288
Domed calvaria, in hamsters, 223, 327
Doramectin, 249, 250
Dohle bodies, rodents, 124
Doxycycline hyclate, dosages/uses for, 143t, 145t, 200, 312
Doxapram, dosages/uses for, 153, 155
Droncit, 260
Drugs
antimicrobials
hamsters, gerbils, mice, rats, 145t, 155
rabbits, guinea pigs, chinchillas, 142, 143t
antiparasitic agents
hamsters, gerbils, mice, rats, 145t
rabbits, guinea pigs, chinchillas, 143t, 144t
general information, 142
toxicities, 142
"Drumstick" body,. *See* Barr bodies, guinea pigs
Duncan-Hartley guinea pigs, 45
Dust bath
chinchilla, 57, 58, 59, *61*, 62, 63, 220
gerbil, 77, *77*, 228
Dysbiosis, 33, 34, 142, 155, 202, 213, 223, 226, 277, 349
Dyspnea
gerbils, 229
guinea pigs, 214, 215t, 257
hamsters, 224, 225t
mice, 233, 234t
rabbits, 204, 205t, 290, 329, 337
rats, 239–240, 239t, 333
Dystichiasis, rabbits, 136
Dystocia
chinchillas, 63, 221
guinea pigs, 217, 218t
mice, 236
rabbits, 41, 54
rodents, 180
Dystrophic mineralization, 208, 209t, 217, 218t, 290

E

Ear mites, rabbits, 200, 205, 211, 246, 247–249, *247*
Ear notch-punch code, identification of mice, 13, *14*

Ectromelia virus, 232, 307–309
Ectropion, rabbits, 138, 207, 208
EDIM, *See* Rotavirus infections
Ehlers-Danlos syndrome, 200
Eimeria caviae, 263
Eimeria chinchilla, 263
Eimeria falciformis, 263
Eimeria flavescens, 263
Eimeria irresidua, 263
Eimeria magna, 263
Eimeria media, 263
Eimeria nieschulzi, 263
Eimeria perforans, 263
Eimeria piriformis, 263
Eimeria stiedae, 118, 203t, 259, 260–262, *261*,
Ejaculatory plug, mice, 62, 234, 235t
Elizabethan collars, 97, 175, 183, *183*, 190, 288, 317
Embryonal nephroma, rabbits, 208, 209t, 318
Embryonic mortality, rabbits, 32
EMLA cream, 106t, 107, 111, 157
Encephalitis, 102, 206t, 207, 216t, 220, 226t, 229, 234, 240, 241t, 265, 350
Encephalomyocarditis virus, 309
Encephalitozoon cuniculi, 118, 187, 188t, 197t, 207
Encephalitozoonosis (nosematosis), 273–276, *274*
  clinical signs, 274
  diagnosis, 274–275
  etiology, 273
  hosts, 273
  necropsy signs, 274
  predisposing factors, 274
  prevention, 275
  public health significance, 275
  transmission, 273–274
  treatment, 275
Endometrial venous aneurysms, rabbits, 209t, 294
Endotracheal intubation
  guinea pigs, 161–162
  rabbits, 157, 158, *158*, 159, 204
  small rodents, *163*, 166
  technique, 147, 149, 152
Enilconazole, 231
Enrofloxacin
  dosages/uses for, 143t, 145t, 155, 258
  in drinking water, 302
  safety, 142
Enterocolitis, drug-induced, 258
Enteropathies, 276–284
  general discussion, 276–279
  clinical signs, 277
  diagnosis, 277
  etiology, 276
  necropsy findings, 277, *277*
  predisposition, 276–277
  prevention, 277–278
  treatment, 278
Entropion
  rabbits, 136, 138
    surgical treatment of, 178
Enucleation of the eye
  rabbits, 178
Environmental factors, that influence disease, 15
Eperythrozoon coccoides, 332
Epilepsy, in gerbils, 284
Epitheliotropic lymphoma, 200, 318
  gerbils, 228
  hamsters, 222
Epizootic diarrhea of infant mice (EDIM). *See* Rotavirus infections
Equipment needs, 8
  See Instruments
Erythromycin, causing enteric disease, 142, 277
Erythromycin phosphate, dosages/uses for, 145t
Escherichia coli, colibacillosis, 281–283
  clinical signs, 282
  diagnosis, 282
  ETEC/EPEC, 281
  etiology, 281
  hosts, 281
  necropsy signs, 282
  nonenteropathogenic, 280
  predisposing factors, 282–283
  prevention, 282
  public health significance, 282
  rabbits, 34, 209
  transmission, 281
Estrogenic stimulation
  cabbage, 300
  infertility in mice, 233, 235
  infertility in rabbits, 208
  rectal prolapse, 233t
  stimulation Kurloff cells, 48
Ethanol, for pinworms, 325
European brown hare syndrome (EBHS), 337
Euthanasia
  biological and chemical changes due to
    carbon dioxide, 193
    cervical dislocation, 193
    decapitation, 193
    sodium pentobarbital, 193
  general information, 192
  of rabbits, 193
  of small rodents, 194
Exfoliative dermatitis, 200, 201t, 348
Exogenous vitamin C, 254, 298
Exophthalmos, 135
  chinchillas, 139, 220
  rabbits, 207, 259, 136, *136,* 137, 138
  rats, 240

F

F344 rat, 322
  microphthalmia, 140
Facial dermatitis, gerbils. *See* "Sorenose," in gerbils
Facial grimace scoring for pain assessment, 70, 197, *198, 199*
Fatty infiltration, kidney, 208, 209t, 214, 215, 217, 218t
Feeding and food consumption, 12, 13
  chinchillas, 61, 63
  gerbils, 78, 80
  guinea pigs, 50–52
  hamsters, 70
  mice, 87–88
  rabbits, 32–34, 35–36
  rats, 99–100
Fenbendazole, 143t, 146t, 275, 325
Fentanyl/fluanisone. *See* Hypnorm
Fiber, dietary
  requirements, rabbits, 13, 35, 75, 278, 283,
Fibroadenoma, rats, 237, 237t, 322
Fibromas and fibromatosis, 318
Fibrosarcomas, 211, 212t, 222t, 237, 237t
Fighting
  gerbils, 76, 79, 228, 228t
  guinea pigs and chinchillas, 212t
  hamsters, 72, 222t, 223, 225
  mice, 84, *84*, 87, 231, 231t, 232, *232*, 235t, 236, 357
  rabbits, 28, 30, *30*, 32, 179, 201t, 209t
  rats, 95, 237t, 239
Filobacter Rodentiums infections, 269–272, 333
  and *M pulmonis*, 270
  and *P. multocida*, 270
    clinical signs, 270
    diagnosis, 271
    etiology, 269–270
    hosts, 269
    necropsy signs, 270–271
    predisposing factors, 270
    prevention, 271
    public health significance, 271
    transmission, 270
    treatment, 271
Fischer rats
  and SDAV, 268
  leukemia, 322
  Zymbal's gland carcinoma, 237, 237t, 238, *238*
Fixation devices, 179, *182*, 183
Flank glands, hamsters, 66, *66*, 222
Flavibacter/Flexibacter group, 285
Flemish giant rabbits, 21, 334
  and *Pasteurella*, 329
Fluoroquinolones,
  adverse effects, 258
Fly strike, 211, 313, 315. *See* Myiasis
Foa-Kurloff cells. *See* Kurloff cells, in guinea pig blood
Foot hygiene scoring, rabbits, 32, *32*
Formaldehyde gas fumigation, 16, 247, 309, 325, 332
Fracture repair

rabbits, *202*
small rodents, 182, *182*, 183
Fractures
chinchillas, 220
guinea pigs, 216, 216t, 299
rabbits, 7, 29, 179
small rodents, 182, *182*, 183
Francisella tularensis, 197t, 202, 332,
Fumigation, 15,16, 247, 332
Fungi, 63,
dermatophytosis, 272–273
Fur chewing, chinchillas, 8, 220
Fur mites, 187, 192, 212t, 228, 231t, 245–254
Fur ring, chinchillas, 221
"Fur slip,", chinchillas, 59, 62, 220
Furless rabbits, 200
Fusobacterium spp., 200, 201t, 356

G

Gallstones, gerbils, 75
Gamma glutamyl transpeptidase levels, *See* Clinical chemistry
Gangrene, *98*, 232, 238
Gastric dilatation, guinea pigs, 212, *214*, 255
Gastric rupture, rabbits, 287
Gastric stasis in rabbits, 33, 34, 209, 286–288
and low fiber, 34
clinical signs, 287
diagnosis, 287
etiology, 33, 202, 287
hosts, 286
imaging, 130, 133
necropsy, 287, *287*
predisposing factors, 287
postoperative, 157, 255
prevention, 288
treatment, 288
Gastrointestinal diseases, clinical signs and differential diagnoses
chinchillas, 220,
gerbils, 229
guinea pigs, 211–213, 214t
hamsters, 223, 224t
mice, 232–233, 233t
rabbits, 202–204, 203t
rats, 239
Gastrotomy
for hairball removal, rabbit, 176, 288
Gavage, 46, *190*
GDVII virus. *See* Murine encephalomyelitis
Genetically engineered or modified mice (GEM), 1, 2, 4, 5, 5t, 6, 81, 82
Genitourinary conditions and differential diagnoses
chinchillas, 221
gerbils, 230–231
guinea pigs, 217, 218t
hamsters, 225–226, 227t
mice, 234–235, 235t
rabbits, 208–210, 209t
rats, 241, 242t
Gentamicin
adverse fatal reaction to, 142
dosages, 145t
intravitreal, rabbits, 138
toxic effects, 208, 294
Gerbils
anatomic and physiologic characteristics, 75–76
dental anatomy, 180, 181, 182t
as pets
behavior, 6, 76–77
life span, 77
restraint, 77, *77*
behavior, 76
biodata, 80t
color varieties, 75, *75*
disease prevention, 80
feeding and watering, 78
handling and restraint, 76, *76*
health maintenance, 12–13
housing, 77–78, *77*
husbandry, 78
origin and description, 74–75
public health concerns, 80
reproduction
breeding programs, 79
estrous cycle, 79
pregnancy and rearing, 79–80
sexing, 78, *78, 79*
temperature and humidity guidelines, 11t
Giardia muris, 347
Giardiasis, 224t, 232, 233t
Glandular hyperplasia, rabbit, nictating membrane, 207
Glaucoma, 136, 137, *137*, 140, 178, 240
Gliricola porcelli, 212t, 331–332
Glomerulosclerosis, *See* Nephrosis
Glycopyrrolate, 148
Goblet cell hyperplasia, 283, 284
Goitrogens, in cabbage, 51
Golden hamster. *See* Hamsters
Granulomas, 200, 222,
Griseofulvin
dosages/uses for, 143t, 145t, 231
Guide for the Care and Use of Laboratory Animals, 4, 31t
Guinea pigs
allergies to, 16–17, 56, 91
anatomic and physiologic characteristics, 45–48
dental anatomy, 45
dental formula, 45
Kurloff cells in the blood, 48, *48*
palatial ostium, 47, *47*
reproductive tract anatomy, 47–48
as companion animals
behavior, 48–49
handling and restraint, 49, *49*
life span, 49
breeds, 45, *46*
biodata, 55t
disease prevention, 55
feeding and watering, 50–52
vitamin/mineral requirements, 51
hand rearing, 54–55
health maintenance, 12–13
housing, 49–50, *49, 50, 51*
husbandry considerations, 10–11
identification, 13
origin and description, 45
public health concerns, 56
reproduction, 52–55, *54, 55*
breeding programs, 53–55
estrous cycle, 52
neonatal life, 54
palpating for pregnancy, 54
sexing and anatomy, 52–53, *52, 53*
research, uses in, 56
temperature and humidity guidelines, 11t
used as food, 45
varieties, 45–46, *46*
Gyropus ovalis, 212t, 331–332

H

Haemobartonellosis, 332
Haemodipsus spp., 332
Haemophilus spp., 249, 340
Hair chewing
chinchillas, 220
mice, 84, *84*, 230
rabbits, 34, 35, 200
Hairballs. *See* Trichobezoars
Hairlessness, hereditary. *See* Alopecia
guinea pigs, 211, 211t
hamsters, 222t
mice, 231t
rabbits, 200, 201t
Hair pulling, rabbits, 200
Hair ring, penile, in chinchillas, 221
Hamsters
anatomic and physiologic characteristics, 66–68
dental anatomy and formula, 66
flank gland, 66, *66*
as companion animals
behavior, 68
handling and restraint, 69, *69, 70*
life span, 69–70
biodata, 73t
cheek pouches, 67, *67*
Chinese hamster, 66, *66*
color varieties, 66, *66*
disease prevention, 72
environment, 10–11
feeding and watering, 70
housing, 4, 11, 69–70, *70*
husbandry, 10–12
inbred strains, 65, 68t
origin and description, 65

Hamsters *(Continued)*
physical comfort, 10–12
public health concerns, 72–73
reproduction
breeding programs, 71–72
estrous cycle, 72
pregnancy and rearing, 72
sexing and anatomy, 71, *71*
research, uses in, 73
Siberian hamster, 66, 66
temperature and humidity guidelines, 11t
Hantaan virus, 288–289
Hanta virus infections, 288–289
clinical signs, 289
diagnosis, 289
etiology, 288–289
hosts, 288
predisposing factors, 289
prevention, 289
public health significance, 289
transmission, 289
Hantavirus pulmonary syndrome (HPS), 288
Harderian gland, 136, 138, 139
gerbils, 75, 229, 317
lesions, 229
rats, 94, 140, 239, 240, 267–269
Hartley guinea pigs, 45
Hay
allergies, rabbits, 204, 205t
and salmonellosis, 343
as food, 7, 9t, 13, 30, *30*, 33–34, 35,36, 61, 63, 69, 184, 254, 255, 288, 306
moldy, 330
prevents uroliths, 358
Head tilt. *See* Torticollis
Health maintenance, 12
Health Research Extension Act, 4
Heart conditions, 290–291
Heat prostration (stress, stroke), 291–292
chinchillas, *60*, 221
clinical signs, 291
diagnosis, 292
etiology, 291
hosts, 291
necropsy signs, 291
predisposing factors, 2910
prevention, 292
treatment, 292
Helicobacter bilis, 292
Helicobacter hepaticus, 292–293
Helicobacter infections, 292–294
and hepatic tumors in A/J mice, 292
clinical signs, 232, 233t, 292
diagnosis, 187, 293
etiology, 292
hosts, 292
necropsy signs, 293
predisposing factors, 292
prevention, 293
public health significance, 293
transmission, 293
treatment, 293
Hemangiomatosis, 294
Hemangiosarcomas, hamster, 320
Hemaphysis leporipalustrus, 200
Hematology, general discussion, *See* Clinical chemistry
Hematuria and pigmented urine, 294–295
clinical signs, 269, 295
diagnosis, 295
etiology, 294
hosts, 294
necropsy signs, 295
predisposing factors, 294–295
prevention, 295
rabbits, 208
treatment, 295
Hemodipsus ventricosus, 200
Hemorrhagic diathesis, parvovirus, 327
Hemorrhagic fever with renal syndrome (HFRS), 288–289
Hepatic coccidiosis, rabbits, 118, 119, 121, 202, 204, 260–263
Hepatic lipidosis
and obesity, 203t
and pregnancy toxemia, 367–368
in anorectic rabbits, 202
with gastric stasis, 287
Hepatic origin ALT, rats
Hepatic sarcoma, *Taenia* induced, 259
Hepatic tumors, with *Helicobacter*, 292
Hepatitis E infections in rabbits
Hepatoencephalomyelitis virus. *See* Reovirus type 3 infections
Herniation, intestinal, 160, 176, 209t
HFRS. *See* Hantavirus infections
History, 3 (also see individual species)
Housing, 8, (also see individual species)
considerations based upon use, 10–11, *10*
Incisor overgrowth. *See* Dental disease.
Howell Jolly bodies, rats and mice, 122
Humidity
and cestode ova, 260
and heat stroke, 291
low and ringtail, 231, 238
Husbandry (also see individual species)
disinfection, 15–16
health maintenance, 8, 12
housing, 10
identification, 13–15
nutrition, 12–13
physical comfort, 11–12
"Hutch bum" or "Hutch burn," 356
Hydrogen peroxide, 15, 16, 247, 325
Hydromorphone, dosages/use for, 171, 172
Hydrometra, mice, *236*
Hydronephrosis
mice, 236
rabbits, 208, 2094
rats, 241, 242t, 322
Hymenolepis diminuta, 223, 258–260
Hymenolepis nana. See Rodentolepis
Hyperadrenocorticism
gerbils, 228, 229
hamsters, 225
Hypercholesterolemia, gerbils, 229
Hyperkeratosis and mites, 246
Hyperparathyroidism, secondary, 121, 216
Hypervitaminosis A, rabbits, 208, 209t
Hypervitaminosis D, 121, 209t, 218t
Hypnorm (fentanyl/fluanisone), 148, 161
chinchillas, 163
gerbils, 164
guinea pigs, 162
hamsters, 163
mice, 166
rabbits, 107, 150t, 161
rats, 164
small rodents, 148
Hypochlorite, 15, 273, 309, 356,
Hypothermia, during surgery and imaging, 134, 153,157, 164, 174, 196
Hypovitaminosis A, D, E, 208, 209t, 240, 305,
Hypovitaminosis C (scurvy) in
guinea pigs, 212, 215, 298–301, 350
clinical signs, 298–299
diagnosis, 299
etiology, 298
hosts, 298
necropsy signs, 299
predisposing factors, 298
prevention, 300
treatment, 300
oral vitamin C tablet, 187
vitamin C content food, 300t

I

Identification methods, 13–15, *13*, *14*
Idiopathic vasculitis, mice, 234
IDIR. *See* Infectious diarrhea of infant rats (IDIR), 342–343
Ileal hyperplasia, 301
Ileus, and anesthetics, 165, 175, 179, 241
Immune-mediated exfoliative dermatosis (Dutch rabbits), 200
Immune complex glomerulonephritis, 127, 304
Impaction
guinea pigs, feces, 213
seminal vesicles, 235
Incoordination and seizures
gerbils, 229
guinea pigs, 215
mice, 234
rabbits, 207, 336
rats, 240
Individual ventilated caging (IVC), 11, *See* Housing
Induced ovulators, 38, 318
Infectious diarrhea of infant rats (IDIR), 342–343

Infertility
causes of, 359
gerbils, 78, 230
guinea pigs, 217, 218t
hamsters, 226
mice, 235
rabbits, 20, 25, 32, 209t
rats, 241
Inguinal canals, 180
Inherited corneal dystrophy, Dutch rabbits, 137
Insecticides (organophosphates), 206t, 207
Instruments, general, 8, 9t, 174
Intestinal flora, rabbits, 34
Intestinal herniation, guinea pig, 176, 217
Intraosseous cannulation, *155*, 174, 191, 255, 278
Intravenous catheter, placement, 114, 149, *154, 155*, 174, 330
Intussusceptions
hamsters, 223
with pinworms, 324
Ionophores, toxicity, 262
Isoflurane
for anesthesia, 107, 120, 130, 132, 134, 148, 154, *154*, 158, *158*, 160t, 161, *161*, 163, 164, 166
for euthanasia, 193, 194
IV fluid therapy, *156*
Ivermectin
dosage/uses for, 144t, 146t, 248, 249, 250, 252, 325, 358

K

Kanamycin, uses, 349
Keratin plugs, gerbil ears, 229
Keratitis sicca, and SDAV, 268
Keratoconjunctivitis, 136, 139, 240
Ketamine
combinations, 151t, 159, 162, 163, 165, 166
CRI, 160t, 288,
dosages, imaging, 130, 134
injury, small rodents, 149
hematology, chinchillas, 122
Ketamine and diazepam, 160, 162, 163, 164
Ketamine and midazolam, 149
Ketamine and xylazine
corneal damage due to hypoxemia, rats, 140, *140*, 154, *154*
rabbits, 160
Ketoacidosis, 210. *See* Pregnancy toxemia or ketosis
Ketoconazole, dosages/uses for, 145t
Ketonuria, 128, 336
Ketosis, 127, 215, 226, 254, 336–337
Kirschner wires, 183
Klebsiella oxytoca, mice, 235
Klebsiella pneumoniae
chinchillas, 220
rabbits, 204, 205t
Knock out technology, 5t, See Genetically Modified Mouse
Kurloff cells, in guinea pig blood, 48, *48,* 124

L

Lactobacillus spp, 276
Lactobacillus, acidophilus, 282
Lactobacillus, bulgaricus, 282
Laryngeal mask airway, 10t, 148, 153, 159, *159*
Laryngoscope, 152, 158, 162
Laryngoscope blade, 158
Laryngospasm, 149, 160t
L-ascorbic acid. *See* Hypovitaminosis C
Lawsonia intracellularis, 202, 203t, 224t, 276
Lawsonia infections (proliferative ileitis of hamsters), 301–302
clinical signs, 301
diagnosis, 301
etiology, 301
hosts, 301
necropsy signs, 301
predisposing factors, 301
prevention, 302
public health significance, 302
transmission, 301
treatment, 302
Leiomyoma, 217, 218t, 235, 242t, 320
Leporacarus gibbus 200, 201t, 247, 249
Lethal intestinal viral infection of mice (LIVIM), 342
L-gulonolactone oxidase, 51, 298
Lice. *See* Pediculosis
Lidocaine hydrochloride
CRI, rabbits, 157
for endotracheal intubation, 149
for epidural anesthesia, rabbits, 157
Lime sulfur dips, 143t, 144t
Lincomycin
contraindications for, 142
enterotoxemia in rabbits, 258, 277, 279
uses, 350
Lipid keratopathy, 137, 207
Liponyssoides sanguineous, 228
Listeria monocytogenes, 206t, 208, 302–303
Listeriosis, 302–303
clinical signs, 302
diagnosis, 302
etiology, 302
hosts, 302
necropsy signs, 302
predisposing factors, 302
prevention, 303
public health significance, 303
transmission, 302
treatment, 302–303
Listrophorus gibbus, see Leporacarus gibbus
Litter desertion or death of neonates
gerbils, 230
guinea pigs, 217
mice, 236
rats, 241
Liver lobe torsion in rabbits, 303
LIVIM, 342. *See* Lethal intestinal viral infection of mice (LIVIM)
Long Evans rats, 94, *94*
Low stress handling, 95, *95, 96*
Lymphademitis, and *Salmonella*, 344
Lymphadenopathy, guinea pigs, 212t, 351–352
Lymphocytic choriomeningitis (LCM) virus, infection, 303–305
clinical signs, 304
diagnosis, 323
etiology, 304
hosts, 303
necropsy signs, 304
predisposing factors, 304
prevention, 304
public health significance, 304
transmission, 304
Lymphocytic leukemia, in guinea pigs, 319
Lymphoma, 117, 138, 201t, 207, 208, 210, 215, 223, 238, 320, 321
epitheliotropic, 222, 228, 231

M

Macrolide antibiotics, cautions, 277
Magnetic resonance imaging, 130, 134
Maggots, 201, 313–315, 315
Male reproductive conditions
guinea pigs (and chinchillas), 218t
hamsters, 227t
mice, 235t
rabbits, 209t
rats, 242t
Malocclusion and dental disease, 305–307
and anorexia, 254
and oral ulcers, 255
chinchillas, 183–184, 220
clinical signs, 306
etiology and predisposing factors, 305
guinea pigs, *47*, 212, *213*, 215, 300, *305*
hamsters, 66, *67*, 223
hosts, 305
mice, 232
prevention, 306
rabbits, 23, *23*, 34, 131, *131*, 184
rats, 239
treatment, 306
Mammary adenacarcinomas, 211, 212t, 222t, 226, 231, 231t, 235, 321
Mammary fibrodenoma, rats, 237t, *238*, 322
Mammary gland conditions
guinea pigs (and chinchillas), 217, 218t
hamsters, 227t
mice, 235t
rabbits, 200, 201t, 209t
rats, *238*, 242t, 322

Mammary tumors, 182, 320–322
Mastitis, 307
  etiology, 307
  hosts, 307
  predisposing factors and clinical signs, 307
  treatment and prevention, 307
Mastocytoma
  in gerbils, 228
  in hamsters, 222
Maxilene cream, 107, 157
Mebendazole
  dosages/uses for, 146t, 260
Medetomidine
  dosages/uses for, 151t, 153, 158, 159, 160, 161, 164, 165, 166
Medical imaging
  computed tomography scanning, 130, 134
  general information, 130
  medical resonance imaging, 130, 134
  radiography, 130–134
    contrast, 133
    rabbits, 130, *130, 131, 132*
    rodents, 132–133
  ultrasonography, 133–134
Megaloileitis, 355
Meloxicam, 170, 171t, 172, 172t, 249, 288,
Meriones unguiculatus. See Gerbils
Mesocricetus auratus. See Hamsters
Metastatic mineralization, or calcification
  guinea pigs, 294
Methacillin-resistant *Staphylococcus*, 349
Metritis
  guinea pigs, 218t
  hamsters, 227t
  Listeria, 302
  mice, 235
  M. pulmonis, rats, 241, 311
  S. pneumoniae, 350
  rabbits, 41, 204, 208, 209t, 217
  Treponema, 359
Metronidazole
  dosages/uses for, 143t, 145t, 178, 184
  treatments, 278, 293, 302
Mice
  allergies to, 16–17, *16*
  anatomic and physiologic characteristics, 82–83
    dental anatomy, 82, *83*
  as companion animals, 84
  behavior, 84
  barbering/whisker trimming, 84, *84*
  behavior, 84
  biodata, 92t
  body condition scoring, *88*
  disease prevention, 15–16, 91,186
  environmental improvement, 11, *86, 88*
  feeding and watering, 12–13, *12*, 87–88
  genetic characteristics, 81
  genetic engineering, 4–6
  genome, 82
  handling and restraint, 85, *85, 86*
  health maintenance, 12
  housing, 10–11, 85, 87 *86, 87*
  identification, 13–14, *13, 14*
  inbred mouse strains, 82
  knockout technology, 4 *5*
  lifespan, 84
  microbial classification, 82
  origin and description, 81–82
  physical comfort, 11–12
  public health concerns, 91
  pygmy mice, 82
  reproduction
    breeding programs, 89–90
    estrous cycle, 88
    pregnancy and rearing, 90–91, *90*
    sexing, 88, *90,*
  research, uses in, 91
  temperature and humidity guidelines, 11t
  transgenic, 4
Microphthalmia
  mice, 234
  rats, 140, 240
Microsporum canis, 210t, 272,
Microtus spp., 82, 288
Microwavable heating pads, 9, 153, *153*
Midazolam
  dosages/uses for, 107, 113, 130, 134, 148, 149, 150t, 158, 159, 162, 163, 164, 165, 166
Milk enterotoxemia, 280
"Milky way" liver, 354
Mineralization
  cerebral, 327
  corneal, 140
  guinea pigs, 138, 217, 218t, 294
  myocardial, 233, 290
  renal failure, 121, 208
Minerals, requirements, rabbits, 35–36
Mitaban. *See* Amitraz
Mite infestation. *See* Acariasis
MNV. *See* Murine norovirus infections
Moist dermatitis. *See* Ulcerative dermatitis
Molting, rabbits, 200, 201t, 287
Mongolian gerbil. *See* Gerbils.
Monogamous pairs, gerbils, 74
Mosquitoes
  and myxomatosis, 316
  and tularemia, 353
Mouse hepatitis virus (MHV), 186, 232, 265–267
Mouse leukemia virus (MULV), 321
Mouse mammary tumor virus (MMTV), 231, 235
Mouse minute virus (MMV), 326–328
Mouse parvovirus (MPV), 326–328
"Mouse polio." *See* Murine encephalomyelitis.
Moxidectin, 146t, 231, 246, 249, 252
MRI, 130, 134
Mucoid enteropathy, of rabbits 202, 203t, 277, 283–284
  clinical signs, 283
  diagnosis, 283
  etiology, 283
  hosts, 283
  necropsy signs, 283, *284*
  predisposing factors, 283
  prevention, 284
  public health significance, 284
  transmission, 303
  treatment, 28
Mucopurulent rhinitis, rabbits, 204, 329, *329*
Multivitamins, 294, 299
Murine encephalomyelitis, 309–310
  clinical signs, 310
  control and prevention, 310
  diagnosis, 310
  etiology, 309
  hosts, 309
  necropsy signs, 310
  public health significance, 310
  transmission, 309
Murine leukemia virus (MULV), 321
Murine mycoplasmosis, 310–312
  clinical signs, 311
  diagnosis, 333
  etiology, 310
  hosts, 310
  necropsy signs, 311, *311*
  predisposing factors, 310
  prevention, 312
  public health significance, 312
  transmission, 310
  treatment, 311
Murine norovirus (MNV-1) infections, 312–313
  clinical and necropsy signs, 313
  diagnosis, 313
  etiology, 312
  hosts, 312
  predisposing conditions, 312–313
  public health significance, 313
  transmission, 312
Mus musculus. See Mice
Mycobacterium spp., hamsters, 222
Mycoplasma arthritidis, 310
Mycoplasma pulmonis, 310–313
Myiasis (fly strike)—primary, 313–315
  clinical signs, 314
  diagnosis, 314
  etiology, 313
  hosts, 313
  necropsy signs, 314
  predisposing factors, 314
  prevention, 314
  public health significance, 314
  transmission, 314
  treatment, 314
Myiasis (fly strike)—secondary, 315

clinical signs, 315
diagnosis, 315
etiology, 315
hosts, 315
predisposing factors, 315
prevention, 315
public health significance, 315
transmission, 315
treatment, 315
Myobia musculi, 231, 246
Myocardial degeneration
gerbils, 229
mice, 233
rabbits, 290
Myocardial fibrosis, rats, 239
Myocardial mineralization, DBA mice, 233
Myocarditis, 229, 264, 290
Myocardium, fatty infiltration, 214
Myocoptes musculinus, 91, 231, 246
Mystromys albicandatus, 339
Myxofibromas, 318
Myxomatosis, 42,137, 201t, 204, 205t, 207, 315–316, 318
clinical signs, 316
diagnosis, 316
etiology, 316
hosts, 314
necropsy, 316
prevention, 316
transmission, 316
treatment, 316

N

Nalorphine, dosages/uses for, 153
Naloxone, dosages/uses for, 150t, 161, 162, 170, 172
Nasal dermatitis (sore nose) in gerbils, 228, *229*, 317
Nasal discharge
gerbils, 229
guinea pigs (and chinchillas), 215t, 298, *298*
hamsters, 224, 225t,
mice, 233, 234t
rabbits, 37, 204, 205t, 329, *329*, 338
rats, 239, 239t
Nasolacrimal duct blockage rats, 240
Nasolacrimal duct flush, rabbits, 136, 192, 330
Necrotic hepatitis of rabbits. *See* Viral hemorrhagic disease (VHD) in rabbits
Neisseria spp., 204
Neophobia, food, 254
Neoplasia, 317–322
chinchillas, 319
general discussion, 317
gerbils, 320
guinea pigs, 319
hamsters, 319–320
mice, 320–321
rabbits, 318–319
rats, 321–322
Nephrocalcinosis, rats, 241
Nephrosis, 322–324
clinical signs, 323
diagnosis, 323
etiology, 322–323
gerbils, 229
hosts, 322
necropsy signs, 323
predisposing factors, 323
prevention, 323
rats, 94, 241, 322
transmission, 323
treatment, 323
Nervous and musculoskeletal
conditions and differential diagnoses
guinea pigs and chinchillas, 216t
hamsters, 226t
rabbits, 206t
rats, 241t
Nest boxes
rabbits, *39,* 40, 40, 41, 42
Nest building, hamsters, 72
Nictating membrane, 136, 138
lymphoid hyperplasia of, rabbits, 178
Nitrate toxicity, rabbits, 208
Nonaversive handling practices
Norway rat. *See* Rats
Notoedres cati, 222t, 223
Notoedres muris, 273t
Nude mouse strains, *63*, 337
Nutrition
general rules, 12–13
requirements, rabbits, 32–33

O

Obesity
constipation, 202, 213, 223
fiber, in rabbits, 35, 51
heat prostration, 291
in guinea pigs, 51
ketosis or pregnancy toxemia, 202, 336
overfeeding, 13
pododermatitis and, 334, 335
reducing, in rabbits, 34, 35, 255
Ocular diseases, clinical signs and differential diagnoses *See* Ophthalmology
chinchillas, 220–221
gerbils, 229
guinea pigs, 217
hamsters, 225
mice, 234
rabbits, 207–208, *208*
rats, 240, *240*
Onychomys See Mice
Ophthalmology, 135–141
chinchillas, 139
equipment and methods, 135–136
general information, 135
gerbils, 139, *139*
guinea pigs, 138–139, *139*
hamsters, 139
mice, 139–140
rabbits, 136–138, *136, 137*
rats, 139–140, *140*
Oral administration of substances, 189–191, *189, 190*
esophagostamy tube placement, rabbit, 190
gavage, 189, 190, *190*
esophageal rupture secondary to, 190
nasogastric tube placement, rabbit, 190, *190*
Orchidectomy
guinea pig, *181*
rabbit, 176–177, *177*
rodents, 180–181
Orchitis, 176, 209t, 218t, 227t, 235t
Organophosphates
mites, 246
toxicity, 236
Ornithonyssus spp, 102, 238, 250, 241
Orthopedic procedures, rabbits, 179
Orthopox virus, 308
Oryctolagus cuniculus, see Rabbits
Osseous choristoma, 217
Osteoarthritis
guinea pig, 216, 216t
hamster, 226t
rabbit, 206t, 207
rat, 240, 241t
Otitis interna, 220, 229, 234, 240
Otitis media
and *Bordetella,* 247
and *Encephalitozoon* infection, 274
and *M. pulmonis,* 240, 241t, 311
and mites, 248
and *S. pneumoniae,* 350
Ovarian cysts
gerbils, 228t, 230
guinea pigs, *134*, 211, 212t, 217
Ovarian tumors, mice, 320
Ovariectomy, small rodents, 181
Ovariohysterectomy
rabbit, 175–176
rodents, 180
Oxytetracycline
dosages/uses for, 143t, 145t, 344, 349, 350, 355
Oxytocin, dosages/uses for, 41, 54
Oxyuriasis (pinworms), 324–326
clinical signs, 223, 324
diagnosis, 325, *325*
etiology, 324
hosts, 324
impact on research, 325–326
necropsy signs, 324
predisposing factors, 324
prevention, 325
public health significance, 325
transmission, 324
treatment, 325

P
Pain
  analgesia, 169–174
  facial grimace scoring, 197, *198, 199*
  manifestations of, 25, 32, 68, 76, 84, 95
  recognizing signs of, 196–200, *197*
Palatal ostium
  guinea pig, 46, *47*, 149
Panalog, 249
Pancreatitis, 119, 240
Panophthalmitis
  and *Rodentibacter* complex infections, 234, 340
  guinea pigs, 138, 217
Parainfluenza type 1, 345–346
Parainfluenza virus, guinea pigs, 214
Paralysis
  guinea pigs (and chinchillas), 215, 216, 216t, 298
  hamsters, 226t
  rabbits, 206t, 207, 280
  rats, 240 241t
Paramyxovirus, 345–346
Paraphimosis, in chinchillas, 221
Paresis
  guinea pigs (and chinchillas), 215–216, 216t
  hamsters, 226t
  rabbits, 206t, 207
  rats, 240, 241t
Parvovirus infections, 326–328
  clinical signs, 327
  diagnosis, 327
  etiology, 356
  hosts, 356
  impact on research, 328
  necropsy signs, 327
  predisposing factors, 327
  prevention, 327
  transmission, 356
  treatment, 328
PAS reaction, 273, 333, 347, 355
Passulurus ambiguus, 202, 324–326
Pasteurella multocida infections, 328–331
  clinical signs, 329
  diagnosis, 329–330, *329*
  etiology, 331–332
  hosts, 328
  necropsy signs, 329, *330*
  predisposing factors, 329
  prevention, 329–330
  public health significance, 3330
  transmission, 329
  treatment, 329
Pasteurella pneumotropica infections, see *Rodentibacter* complex
"Pea eye", guinea pigs, 138, *139*, 217
Pediculosis, 331–332
  clinical signs, 331–332, *332*
  diagnosis, 332
  etiology, 331
  hosts, 331
  predisposing factors, 331
  prevention, 332
  public health significance, 332
  transmission, 331
  treatment, 332
Penicillin, and enterotoxemia, 142
Penicillin G, dosages, 143t
Permethrin, dosages/uses for, 146t
Peromyscus maniculatus, 288
Peyer's patches
  and coccidiosis, 264
  and low protein diet, 277
  and mouse pox, 308
  and salmonellosis, 344
Phacoclastic uveitis, 135, 138, 207
Phenol red thread tear test, 135
  rabbits, 136
Phenotyping, *See* genetically modified mice
Phycomycosis, 240
Physical comfort, 11–12
Physiologic values, See Biodata
Picornaviridae, 309
Pigmented urine, *See* Hematuria
Pine bedding and volatile oils, 147
Pinworms. *See* Oxyuriasis
Piperazine, dosages/uses for, 325
Pituitary adenoma
  rabbits, 200, 201t, 205, 206t
  rats, 240, 241t, 322
Pituitary dwarfism, and LCMV, 304
Placentitis, 302
Plant toxicosis, 294
Pneumococcus spp., 350
Pneumocystis carinii, 240
Pneumocystosis, 332–334
  clinical signs, 333
  diagnosis, 333
  etiology, 332–333
  hosts, 332
  necropsy signs, 333
  predisposing factors, 333
  prevention, 333
  public health significance, 333
  transmission, 333
  treatment, 333
Pneumonia
  chinchillas, 221
  gerbils, 229
  guinea pigs, 215, 215t, 217
  hamsters, 224, 225t
  mice, 233, 234t
  rabbits, 131, 204, 205t, 209, 210
  rats, 239, 239t
Pododermatitis, 334–335
  clinical signs, 334, *334*
  diagnosis, 334
  etiology, 334
  hosts, 334
  predisposing factors, 334
  prevention, 335
  scoring, *335*
  treatment, 334
Polyarthritis, rats, 310
Polycystic disease
  hamsters, 227t, 323
  rats, 241
Polyoma virus, 320, 321
Polyplax *serrata*, 331–332
Polyplax spinulosa, 331–332
Polyradiculoneuropathy, rats, 240
Porphyrins
  gerbils, 75, 317
  rabbits, 32, 294
  rats, 94, 140, 311
Poxviridae, 308
Praziquantel, dosages/uses for, 144t, 260
Preeclampsia, 336
Pregnancy (ketosis) toxemia, 336–337
  clinical signs, 336
  etiology, 336
  guinea pigs, 212, 214t, 215, 216t, 217, 218t
  hosts, 336
  necropsy signs, 336
  predisposing factors, 336
  prevention, 336
  rabbit, 122, 202, 203t, 206t, 207, 208, 209t, 210
  treatment, 336
Prenatal mortality
  gerbils, 230
  guinea pigs, 217
  hamsters, 226
  rabbits, 208
Preputial dermatitis, guinea pigs, 211
Preputial gland abscesses, mice 235t
Prolactin-secreting tumors, 205, 237
Prolapse
  guinea pigs, uterine, 217
  hamsters, 139, 223
  Harderian glands, 229
  mice, 232, 233t, 236
  rabbits,
    third eyelid gland, 136, *136*, 138, 209t
  rats, 241
Proliferative ileitis, (*Lawsonia* infections) in hamsters, 301–303
Proptosis, hamsters, 225
Prostatitis, rats, 241
Prostigmata, 247
Proteus spp.,
  and guinea pig conjunctivitis, 138
Pruritis
  and dermatophytes, 272
  and lice, 331
  guinea pigs, 249
  hamsters, 250
  rats, 253
Pseudohibernation, hamsters, 67
Pseudomonas aeruginosa,

guinea pigs, 215t
mice, 91,
rabbits, 136, 200, 201t, 207
Pseudopregnancy, rabbits, 72
Pseudopterygium. *See* conjunctival overgrowth, rabbits, 138, 178
Pseudotuberculosis, 269–270, *See* *Corynebacterium kutscheri* infections
Psorergates spp., 251, 252
Ptyalism (excess salivation), 305–306
chinchillas, 220
guinea pigs, 214t
rabbits, 202, 203t, 356
Pulmonary adenoma, rats, 240
Puumala virus, 288
Pyelonephritis, 120, 294–295, 322–323
gerbils, 230
guinea pigs, 218t
hamsters, 227t
mice, 234, 235t
rabbits, 208, 209t
rats, 241, 242t
Pygmy mice, 82
Pyocyanin, 356
Pyogranulomatous bronchopneumonia, rats, 286

Q

Q fever, and *Ornithonyssus* spp., 238
Quaternary ammonium residues, 15
and rabbit deaths, 210
Quinolones, and arthropathies, 142, 330

R

Rabbit louse (*Haemodipsus*), 331–332
Rabbit plague. *See* Rabbit viral hemorrhagic disease
Rabbit pox, 204
Rabbit syphilis. *See* Venereal spirochetosis
Rabbit viral hemorrhagic disease, 337–339
clinical signs, 337
diagnosis, 338
etiology, 337
hosts, 337
necropsy signs, 338, *338*
predisposing factors, 337
prevention, 338
public health significance, 338–339
transmission, 337
treatment, 338
Rabbits
allergies to, 16–17
anatomic and physiologic characteristics, 22–24
dental anatomy, 23, *23*, *24*
gastrointestinal anatomy, *24*
anesthesia, 157–161
as companion animals
behavior, 25
life span, 26
handling and restraint, 26–27, *26, 27 28, 29*
biodata, 42t
blood collection, 106–107
body condition score, *38*
bone marrow collection, 114
breeds, *22, 23*
cerebral spinal fluid collection, 114–115
clinical chemistry, 118–121
disease prevention, 15–16, 42
feeding and watering, 33–35
hematology, 116–118, 117t
housing, 27–32
identification, 13, *13*
nasolacrimal duct flushing, 136
nutrient requirements, 35–36
origin and description, 21
public health concerns, 43
reproduction
artificial insemination, 39, *39*
breeding schedules, 39
breeding stock criteria, 36–37
buck criteria, 37
doe criteria, 37–38
group housing production, 40
mating, 38–39
neonatal period, 41
nursing, 41
parturition (kindling), 41
pregnancy, 40
pregnancy detection, 40, *40*
sexing, 36, *37*, *38*
weaning, 42
research, uses in, 43
temperature and humidity guidelines, 11t
urinalysis, 121–122
urine collection, 113, *114*
Rabies virus infection, 339–340
Radfordia affinis, 231, 246
Radfordia ensifera, 237t, 253
Radiography, 130–133
Rapid plasma reagin (RPR) test, 360
Rat coronavirus (RCV), 267–269
Ratbite fever, 91 (*Streptobacillus moniliformis*)
Rats
albino, 94
allergies to, 16–17
anatomic and physiologic characteristics, 94
dental anatomy, 94
as companion animals
behavior, 94–95
life span, 95
handling and restraint, 95–96, *95, 96*
biodata, 102t
disease prevention, 102
feeding and watering, 99–100
housing, 8–12, 96–99
identification, 13
origin and description, 93–94
play/exercise pens, *99, 100*
public health concerns, 102
reproduction
breeding programs, 101
estrous cycle, 100–101
pregnancy and rearing, 101–102
sexing, 100, *100, 101*
research, uses in, 102
stocks and strains, 94, *94*
temperature and humidity guidelines, 11t
Rattus, see Rat
Rectal prolapse, 223, *224*, 292
mice, 232, 233t,
with *Helicobacter* infections, 292
with pinworms, 324
"Red tears", *See* Chromodacryorrhea
"Red nose", *See* "Sore nose", in gerbils
Regulatory considerations, 4
Renal calculi, guinea pigs, 182
Renal cysts, 120
gerbils, 230
guinea pigs, 217, 218t
mice, 234
rabbits, 209t
rats, 241
Renal conditions, *See* Nephrosis
gerbils, 229–230
guinea pigs (and chinchillas), 217, 218t
hamsters, 225, 227t
mice, 234–235, 235t
rabbits, 209t
rats, 241, 242t
Renal failure, induced, 294, 323208,
Reovirus, 232, 233, 265, 353
Reportable diseases
Ectromelia virus, 232
tularemia, 354
Retained placenta, rabbits, 208, 359
Retinal degeneration, mice and rats, 11, 98, 140, 234
Retroviruses, 321
Retrobulbar abscess, 135, *136*, 139, 178, 207, 220, 225
Rhabdomyomatosis, in guinea pigs, 214, 319
Rhinitis
guinea pigs (and chinchillas), 214, 215t
hamsters, 224, 225t
mice, 233, 234t, 345
rabbits, 136, 204, 205t, 328, *329*, 330
rats, 239, 239t
Ribavirin, 200
Ringtail, 339–340
clinical signs, 340
diagnosis, 340
etiology, 339
hosts, 339
mice, 231
predisposing factors, 340
prevention, 340
rats, 238
treatment, 340

Ringworm. *See* Dermatophytosis (ringworm)
Robenidine, 262
Rodentibacter Complex Infections, 340–341
  clinical signs, 340–341, *341*
  diagnosis, 341
  etiology, 340
  hosts, 340
  necropsy signs, 341
  predisposing factors, 340
  prevention, 341
  public health significance, 341
  transmission, 340
  treatment, 341
Rodentolepis nana, 258–260
Roof rat, 94
Rotavirus infections, 256, 342–343
  clinical signs, 342
  diagnosis, 342
  etiology, 342
  hosts, 342
  mice, 232, 233t, 236
  necropsy signs, 342
  predisposing factors, 342
  prevention, 343
  public health significance, 343
  rats, 239
  transmission, 342
  treatment, 343

S

Salivation, in heat stress, 291
Salmonella spp., 63, 91, 186
Salmonellosis, 343–345
  clinical signs, 344
  diagnosis, 344
  etiology, 343
  hosts, 343
  necropsy signs, 344
  predisposing factors, 343
  prevention, 344
  public health significance, 197, 344
  transmission, 343
  treatment, 344
Sand bath, or dust bath
  chinchilla, 57, 58, 59, *61*, 220
  gerbil, *77*, 228t, 229
Sanitation, 12, 15–16
Sarcoptes scabiei, 248, 249
Schmorl's disease, 200, 201t
Schirmer tear test, 135
SCID mice, 266, 310, 321, 333
Scleral mineralization, guinea pig, 138
Scrotal plug, guinea pigs, 217, 218t
Scurvy. *See* Hypovitaminosis C
Sebaceous adenoma, 182, 320
Seed diets, 229
Seizures (and convulsions). *See* Epilepsy.
  audiogenic, 91
  guinea pigs (and chinchillas), 215, 216t
  gerbils, 74, 75, 76, 164, 229, 285–285
  mice, 234
  rabbits, 121, 206t, 207, 275
  rats, 240, 241t
Selamectin
  uses, 144t, 246, 249, 250, 252, 253
Selenium deficiency, 206t, 207
Seminal vesicle impaction, 235
Sendai virus (SV) infections, 224, 233, 234, 236, 239, 345–346
  clinical signs, 345
  diagnosis, 345
  effect on research, 345
  etiology, 345
  hosts, 345
  necropsy signs, 345–346
  predisposing factors, 345
  prevention, 345
  public health significance, 345
  transmission, 345
Senile atrophy of endometrium, rabbit, 318
Seoul virus, 288
Serologic testing, quality assurance programs for health monitoring
  general information, 186–188
  rabbit and rodent diagnostic serology tests, 187t
Sialodacryoadenitis virus (SDAV) infection, 267–269
  clinical signs, 268
  diagnosis, 268
  etiology, 267
  necropsy signs, 268
  predisposing factors, 267–268
  prevention, 268
  public health significance, 269
  rats, 241, 281–283
  transmission, 267
  treatment, 268
Siberian hamster, 65
Sigmondon rat, 94
Sin Nombre virus, 289
Skinny pig, *46, 212, 213*
"Slobbers," 211, *213*, 356
Sodium pentobarbital
  for euthanasia, 193, 194
Sore hocks, *See* Ulcerative pododermatitis
Sore nose, in gerbils, 228, 229, 317, 348
Spironucleosis, 346–348
  clinical signs, 347
  diagnosis, 347
  etiology, 347
  hosts, 346
  necropsy signs, 347
  predisposing factors, 347
  prevention, 348
  public health significance, 348
  transmission, 346
  treatment, 378
Spironucleus muris, 346
Splayleg in rabbits, *41*, 206t, 207
Spay. *See* Ovariohysterectomy
Sprague-Dawley rats, 94
Staphylococcosis, 348–349
  clinical signs, 348–349
  diagnosis, 349, *349*
  etiology, 348
  hosts, 348
  necropsy signs, 349
  predisposing factors, 348
  prevention, 349
  transmission, 348
  treatment, 349
Staphylococcus spp., 356, 358
Staphylococcus aureus, 136, 200, 253
Streptobacillus moniliformis, 91
  guinea pigs, 351
  mice, 235
  rats, 238
Streptococcus spp, 55,
Streptococcus pneumoniae infections in rodents, 351–352
  clinical signs, 351
  diagnosis, 351
  etiology, 351
  hosts, 351
  necropsy signs, 351
  predisposing factors, 351
  prevention, 351
  public health significance, 351
  transmission, 351
  treatment, 351
Streptococcus pyogenes, 358
Streptococcus zooepidemicus infection, 351–352
  clinical signs, 351
  diagnosis, 351
  guinea pigs, 139, 211, 257
  hosts, 351
  necropsy signs, 351
  predisposing factors, 351
  prevention, 351–352
  public health significance, 352
  transmission, 351
  treatment, 351
Streptomycin, toxic
  as a cause of ascending flaccid paralysis, 142
  toxicity, gerbils, 142
Struvite uroliths, 357
Succinyl sulfathiazole, 262
Sulfadiazine, 258
Sulfadimethoxine, dosages/uses for, 143t, 145t, 262, 264
Sulfamethazine, 143t, 145t 258, 262, 264, 264t, 312, 353
Sulfamethoxine, dosages/uses for, 262
Sulfaquinoxaline, and Tyzzer's disease, 355
  dosages/uses for, 143t, 262, 264t, 331
Supracaudal perianal gland, guinea pigs, 211
Surgery

general information, 174
instruments, 174
rabbits, 174–179
abscess removal, 178
conjunctival hyperplasia, 178
cystotomy, 176
ear canal ablation, 179
enucleation, 178
entropion, 178
gastrotomy, 176
laparotomy, 175
orchidectomy, 176–177
orthopedic procedures, 179
ovariohysterectomy, 175–176
rhinotomy, 178–179
thoracotomy, 179
small rodents, 179–183
abscess removal, 181–182
cystotomy, 182, *182*
fracture repair, 182, *182*
lumpectomy, 182
orchidectomy, 180
ovariectomy, 180–181
ovariohysterectomy, 180
Swellings and masses
gerbils, 228, 228t
guinea pigs (and chinchillas), 211, 212t
hamsters, 222–223
mice, 231–232, 231t
rabbits, 200, 201t
rats, 237, 237t
"Swiss roll" technique, 266
Swiss mice, black, NIH
retinal degeneration, 140
Sylvilagus spp
and myxomatosis, 31, 315
and tularemia, 354
Syphacia spp, 91, *191*, 192, 223, 229, 252, 324, 325, *325*

T

Taenia coenurus, in chinchillas, 220, 259
Taenia pisiformis, 258–260
Taenia serialis, 138, 207
Tail skin loss, or "slip,"
gerbils, 228
rats, 239
Tapeworm infections. *See* Cestodiasis (tapeworm infections)
Telazol, dosages/usage, 163, 208, 209t,
Teratogenesis, drug, 231
Tetracycline
dosages/uses for, 143t, 145t, 330, 349, 355
Theiler's murine encephalomyelitis viruses (TMEV), 309–310
Thiabendazole, dosages/uses for, 143t, 145t
Third eyelid. *See* nictitating membrane
Thumping (stomping) feet, gerbils, 76
Thymic involution, mice, 236
Thymoma
rabbits, 121, 134, 136, 138, 200, 204, 318
Thyroid tumors, 240, 320
Ticks, 304, 353
Toolan's H-1 virus, hamsters, 187
Tooth crown elongation, *133*, 184, 205t, 215, 220,
Tooth root abscesses, 184255, 306
Torticollis, wry neck
gerbils, 230
guinea pigs (and chinchillas), 215, 216t, 350, 351
hamsters, 226t
rabbits, 205, 206t, 274
rats, 241t, 311, 329
Toxins, clostridial, 278
Toxoplasmosis, 63, 205, 206t, 215, 216t
Tracheal stenosis, rabbits, 204, 205t
Transgenic mice, see Genetically Modified Mice
Transmissible ileal hyperplasia in hamsters. *See Lawsonia intracellularis* infection.
Transmissible colonic hyperplasia in mice, 352–353
clinical signs, 352
diagnosis, 352–353
etiology, 352
hosts, 352
necropsy signs, 352
predisposing factors, 352
prevention, 353
public health significance, 353
transmission, 352
treatment, 353
Transport boxes, 70
Treponema spp., 356
Treponema paraluiscuniculi (cuniculi), 137, 201
Treponematosis, 359–360
Trichiasis, rabbits, 136, 137, 207
Trichlorphon, 252
Trichobezoars (hairballs), 202, 287
Trichofolliculoma, 211, 319
Trichophyton mentagrophytes, 272–273
gerbils, 228
guinea pigs, 212t
rabbits, 201, 201t
rats, 237t
Trichosomoides crassicauda, 123, 240, 358
Trimethoprim–sulfa, dosages/uses for, 143t, 145t, 258, 278, 288, 333
Trixacarus caviae, 56, 211, 212t, 249–250
Tularemia, 353–354
clinical signs, 354
diagnosis, 354
etiology, 353
hosts, 353
necropsy signs, 354
predisposing factors, 353
prevention, 354
public health significance, 354
transmission, 353
treatment, 354
Tumors. *See* Neoplasia
Tyzzer's disease, 354–356
clinical signs, 355
diagnosis, 355
etiology, 355
hosts, 354–355
necropsy signs, 355
predisposing factors, 355
prevention, 3355–356
public health significance, 356
transmission, 355
treatment, 3355

U

Ulcerative dermatitis (moist dermatitis), 356–357
Ulcerative pododermatitis, see Pododermatitis
Ultrasonography, 130, 133–134, 133, 134
Urinalysis. *See* Clinical chemistry
Urine collection
rabbits, 113
rodents 113–114
Urine, pigmented. *See* HematuriaHamaturia
Urine scalding, 176, 200, 201
Urolithiasis, 357–359
clinical signs, 358
diagnosis, 358
etiology and predisposing factors, 357–358
hosts, 357
necropsy signs, 358
prevention, 358
treatment, 358
Urticaria, 16, 250
Uterine adenocarcinomas
hamsters, 225
rabbits, 294, 295, 318
prevention of, 173
Uterine venous aneurysms, rabbits, 122, 208
Uterine endometrial hyperplasia, 295
Uterine ischemia, and ketosis, 336
Uterine leiomyoma, guinea pigs, 217
Uterine or vaginal prolapse
guinea pigs, 217, *219*
mice, 236
rabbits, 209t
rats, 241, *242*
Uterine, ovarian conditions
guinea pigs (and chinchillas), 218t
hamsters, 227t
mice, 235t
rabbits, 209t
rats, 242t
Uveitis, 136, 137, 138, 207, 234, 240, 274

V
Vaccinia subgroup, 308, 309
Vaginal closure membrane
  chinchillas, 61
  guinea pigs, 52–53, *53*
Vaginal discharge
  hamsters, 72
  rabbits, 208
Vaginal prolapse. *See* Uterine or vaginal prolapse.
Venereal spirochetosis (treponematosis), 359–360
  clinical signs, 359, *359*
  diagnosis, 360
  etiology, 359
  hosts, 359
  necropsy signs, 359
  predisposing factors, 359
  prevention, 360
  public health significance, 360
  transmission, 359
  treatment, 360
Vent disease. *See* Venereal spirochetosis
Verapamil, hydrochloride
  dosages/uses for
    abdominal adhesion prevention, 175
Viral hemorrhagic disease in rabbits, 337–339
Viral infections
  diagnostic serology tests for, 186–187, 187t
Viruses, *See* under names of viral infections/agents
Vitamin B, 255,
Vitamin C, 298–301
  and anorexia, 254
  content in vegetables, 300, 300t
Vitamin E
  deficiency, hamsters, 70
  deficiency, rabbits, 36
  for ulcerative dermatitis, 357
  rats, 241
Volvulus, gastric, guinea pigs, 212

W
"Walking dandruff," 200, 247
Warthin-Starry silver stain, 286, 301, 355
Wassermann test, 360
Wasting syndrome
  guinea pigs, 212–213
  with MHV, 266
Watanabe heritable hyperlipidemia, rabbits, 119
Watering and water consumption
  chinchillas, 61
  gerbils, 78
  guinea pigs, 50–51
  hamsters, 70
  mice, 87–88
  rabbits, 32–33
  rats, 99–100
Weighing rodents, container, *86*,
Welfare-friendly practices, 6–7
"Wet dewlap" disease, 200, 201, 356
"Wet tail" hamsters, 223, 301
Whitten effect, 88, 100
Wind up, 169
Wistar rats, 94
Wool block. *See* Trichobezoars (hairballs)
Wry neck, *See* Torticollis

X
Xylazine
  dosages/uses for gerbils, 164
  dosages/uses for guinea pigs, 162
  dosages/uses for hamsters, 163
  dosages/uses for mice, 165
  dosages/uses for, rabbits, 151t, 153, 159, 160, 161
  dosages/uses for rats, 166
  precautions for small rodents, 154, *157*

Y
Yellow fat, rabbits, 20205
Yersinia pestis, rabbits, 102, 200, 201t
Yersinia pseudotuberculosis, guinea pigs, 211, 212t
Yohimbine, dosages/uses for, 151t, 153, 160, 163
"Young doe syndrome" (milk enterotoxemia), 280, 281, 349

Z
Zephyr stun gun, 193
Zinc deficiency, 201t, 211, 212t, 222t, 231t
Zoonotic diseases, 197t
Zymbal's gland, tumors, 237, 237t, *238*, 322

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