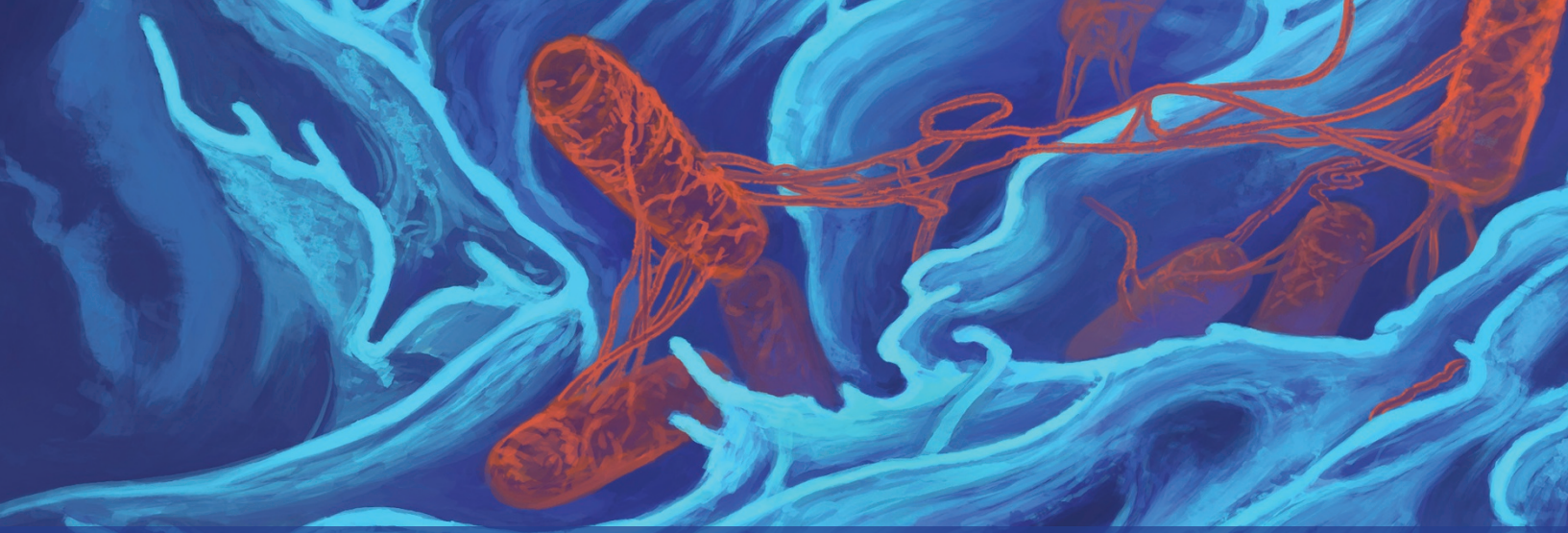

Fourth Edition

Veterinary Microbiology

Edited by **D. Scott McVey, Melissa Kennedy, M.M. Chengappa,** and **Rebecca Wilkes**

with website

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Veterinary Microbiology

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Fourth Edition

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Preface

This collection of chapters and supporting materials is intended to provide a very broad overview of veterinary microbiology and infectious diseases. The writings represent a combination of the biology of the organisms that cause or are associated with disease and the diseases themselves. The scope of this book is intended to be general to appeal both to students of veterinary sciences and to seasoned veterinary practitioners and scientists. Like many textbooks, this book will hopefully serve as a sound foundation for the study of veterinary infectious diseases as well as a good reference text. The content emphasizes diseases that occur in North America, but many global, transboundary diseases are included.

Part I of the book contains chapters that deal with basic microbiology and microbial virulence and parasitism. This chapter is intended to convey a basic knowledge of bacteria, viruses, and fungi to provide a better understanding of specific pathogens and the diseases they cause, which are described in Parts II, III, and IV. Part II describes bacterial pathogens. This section covers a very diverse set of bacterial pathogens and many diseases, but yet the similarities of pathogenesis, virulence properties, and host responses among these organisms are striking. Part III of the book describes in detail mycotic diseases and the fungal pathogens responsible for them. We have tried to emphasize the consequences of fungal infections and the host responses. Part IV deals with important viruses as well as diseases that they cause. We have described the veterinary significance of these diseases, along with methods of diagnosis, prevention and treatment. Part V, the last section of the book, deals with an overview of control of diseases and includes immune response to infectious agents, antimicrobial therapy and resistance, laboratory diagnosis, prophylactic measures with vaccines, and epidemiology and transmission of infectious agents. In the spirit of one medicine, the chapters take a comparative approach to describing both differences and similarities of diseases across many affected species. We have not included the clinical application section which exists in the third edition, as it did not fit well with the format as well as the scope of this book.

This edition contains numerous high-quality figures, which we believe will be very useful for veterinary students in their learning process. This edition will be very beneficial for veterinarians as they render their clinical services in a practice setting.

We have invited a group of outstanding microbiologists/experts/scientists to contribute to this edition. We believe the contents are accurate and up to date. However, we welcome any comments or suggestions that you may have regarding the contents of this book.

D. Scott McVey, Melissa Kennedy,
M.M. Chengappa, and Rebecca Wilkes

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/mcvey/microbiology4

The website includes

- Additional instructional materials for selected chapters
- PowerPoint slides of all figures from the book for downloading
- Videos

Part I

Introduction

1

Microbial Infections of Animals

D. Scott McVey, Melissa Kennedy, and Charles Czuprynski

Veterinary microbiology is the science of infectious agents that affect animals. These agents are categorized by their ecological associations with animals: (i) **parasites** live in permanent association with, and at the expense of, animal hosts; (ii) **commensals** are parasites that cause their host no discernible harm; (iii) **saprophytes** normally inhabit inanimate environments shared with animals; and (iv) **symbiosis,** or **mutualism,** usually refers to reciprocally beneficial associations of organisms. Pathogenic organisms can be either parasites or saprophytes and may cause disease in one or more animal species. The process by which organisms establish themselves in an individual host is termed **colonization** or **infection**. Some infections directly cause or induce deleterious outcomes in a host, whereas others do not and result in what might be called subclinical infection. The term **virulence** is sometimes used to express degrees of pathogenicity, often related to the severity of clinical illness and occurrence of deleterious outcomes (mortality or tissue damage) (Table 1.1).

Some Attributes of Host–Parasite Relationships

Many pathogenic microorganisms are host specific in that they parasitize only one or a few animal species. For example, the cause of equine strangles, *Streptococcus equi* subspecies ***equi***, is essentially limited to primary infection of horses. Other microorganisms – for example, certain ***Salmonella*** serotypes have a broad host range. The basis for differences in host specificity is often incompletely understood but may in part be related to the need for specific attachment mechanisms between hosts (receptors) and pathogens (adhesins).

Some agents infect several host species with varying effects. For example, the plague bacillus *Yersinia pestis* behaves as a commensal parasite in many small rodent species, but causes fatal disease in cats and humans. Evolutionary pressure may explain some of these differences. For instance, ***Coccidioides immitis***, a saprophytic fungus that requires no living host, infects cattle and dogs with equal ease. Yet it produces no clinical signs in cattle, but frequently causes progressive and fatal disease in dogs.

Potential pathogens also vary in their effects on different tissues in the same host. *Escherichia coli* strains that are commensals in the intestine can cause severe disease in the urinary tract and peritoneal cavity. Some microorganisms that are commensals in one habitat may be pathogenic in the same, or some other, habitat that is pathologically altered or otherwise compromised. For example, oral streptococci occasionally enter the bloodstream from which they can colonize a physically damaged heart valve and initiate bacterial endocarditis. In the absence of such a lesion, the streptococci do not colonize and are cleared uneventfully by the innate immune system. Similarly, the frequent translocation of intestinal bacteria across the intestinal mucosa, and into the vasculature channels, normally leads to their clearance by innate and adaptive defense mechanisms. However, in immunodeficient hosts or after overwhelming translocation of large numbers of bacteria, this translocation to the intestinal vasculature can lead to fatal septicemia.

Commensalism is a stable form of parasitic existence. But if a commensal gains entrance into a novel host or tissue, or there is a substantial reduction in host resistance, commensal parasites can become active pathogens that ensure the survival and multiplication of the microorganism. However, active disease can jeopardize pathogen survival by evoking an immune response that eliminates the microorganism, or by overwhelming defense mechanisms that kill the host and restrict further microbial

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Table 1.1 Degrees of pathogenicity.

Saprophytes	No disease – environmental microorganisms
Commensal organisms	Colonize host tissue – no disease
Symbiotic species	Beneficial relationship for the host; colonize host tissue – mutually and parasitic microorganisms
Opportunistic parasites	Colonize host tissue (usually saprophyte or commensal), but under favorable conditions cause disease with tissue damage
Pathogenic microorganisms	Infection directly causes disease (although this may be host specific)

multiplication and transmission (Table 1.1). In general, evolutionary selective pressure tends to select for commensalism and generally eliminates host–parasite relationships that threaten the survival of either partner. Over time, less virulent strains of a pathogen, which permit survival of the host, tend to arise and replace the more lethal strain. Evolutionary selection also favors establishment of a resistant host population by eliminating highly susceptible individuals. One example is in Africa, where regionally adapted livestock are resistant or partially resistant to the protozoal pathogen of theileriosis. Most agents that cause serious disease have alternative modes of survival as commensals in tissues in which they do not cause damage (e.g. uropathogenic *E. coli* in the intestine), hosts less susceptible to disease (e.g. *Y. pestis* in small rodents), or the inanimate environment (e.g. *Crabro immitis*). Some pathogens cause chronic infections lasting months or years (e.g. tuberculosis and glanders disease), which increases the time and opportunities for their dissemination to other hosts that ensures their survival.

Criteria of Pathogenicity – Koch's Postulates

The presence of a microorganism in diseased individuals does not prove its pathogenic significance. To formally demonstrate the causal role of an agent in a disease, the following qualifications or "postulates" of Robert Koch (1843–1910) should be satisfied:

1) The suspected agent is present in all cases of the disease.
2) The agent is isolated from such disease and propagated serially in pure culture, apart from its natural host.
3) Upon introduction into an experimental host, the isolate produces the original disease.
4) The agent can be reisolated from this experimental infection.

These postulates are ideals that cannot always be experimentally verified in all infectious diseases. The presence of some microorganisms cannot be demonstrated at the time of disease, especially in tissues affected by intoxication (e.g. tetanus and botulism). Some agents (e.g. *Mycobacterium leprae*) cannot be maintained in culture apart from their natural hosts. Other pathogens are difficult to isolate or die rapidly after isolation (e.g. ***Leptospira*** spp.). Still others, although clearly pathogenic, often require undetermined accessory factors to cause disease (e.g. ***Pasteurella***-related pneumonias). In addition, contemporary molecular microbiological methods suggest that some infections involve more than one microbial species via interactions that, at this time, might not be understood.

Elements in the Transmission and Production of Infectious Disease

Effective transmission of a microbial agent occurs by ingestion, inhalation, or inoculation of a mucosal or cutaneous surface. Airborne infection takes place largely via droplet nuclei, which are 0.1–5 mm in diameter. Particles of this size stay suspended in air and can be inhaled. Larger particles settle but can be resuspended in dust, which might also harbor infectious agents from nonrespiratory sources (e.g. skin squames, feces, and saliva). Arthropods can serve as mechanical carriers of pathogens (e.g. equine arteritis or African swine fever) or play an indispensable part in the life cycles of disease-producing agents (e.g. plague, ehrlichiosis, and viral encephalitides or hemorrhagic fevers) before inoculating the organism into the skin.

Attachment to host surfaces requires interaction between the agent's adhesins, which are usually proteins, and the host's receptors, which are most often protein or carbohydrate residues. Examples of bacterial adhesins include fimbrial proteins (*E. coli* and ***Salmonella*** spp.), P-1 protein of ***Mycoplasma*** **(***Mycoplasma pneumoniae***)**, and afimbrial surface proteins (some streptococci). Examples of host receptors include fibronectin for some streptococci and staphylococci, mannose for many *E. coli* strains, and sialic acid for *M. pneumoniae*.

Pathogen attachment can be inhibited by commensal organisms that occupy or block available receptor sites or discourage colonization by other microbes via excretion of toxic metabolites, bacteriocins, and microcins. This "colonization resistance" is an important defense mechanism and may be augmented by host-derived antibacterial substances (e.g. defensins, lysozyme, lactoferrin, and organic acids) or by mucosal antibodies that prevent attachment of or damage the invader.

Penetration of an epithelial or mucosal host surface is a variable requirement among pathogens. Some agents, having reached their primary target cell or tissue, do not invade further (e.g. enterotoxigenic *E. coli*). Others traverse epithelial cells by inducing cytoskeletal rearrangements that result in "ruffles," which entrap adhered bacteria or facilitate their passage between epithelial cells (e.g. ***Salmonella*** and ***Yersinia***). Inhalation of facultative intracellular parasites such as *Mycobacterium tuberculosis* results in ingestion by pulmonary macrophages, in which the bacilli may survive, multiply, and travel via lymphatics to lymph nodes and other tissues. Percutaneous penetration by pathogens occurs through injuries, including minor trauma (scratches, etc.) and insect or arthropod bites. Dissemination within tissues, or among adjacent tissues, might involve microbial invasion of host cells, aided in part by bacterial enzymes, such as collagenase and hyaluronidase, that degrade the extracellular matrix and facilitate microbial movement. Once microorganisms breach an epithelial surface (cutaneous or mucosal), they can spread via various "highways" in the host including lymphatic and blood vessels, the bronchial tree, bile ducts, and nerve trunks. Migration within the host can occur both as extracellular microbial cells and after entering and hitching a ride in mobile phagocytes (macrophages and neutrophils).

Except for foodborne pathogens that produce toxins in foodstuffs prior to ingestion (e.g. *Clostridium botulinum* toxins, Staphylococcal enterotoxins), growth in or on a host is a prerequisite for all pathogenic organisms. To do so microbes must circumvent host defense mechanisms. Microbial strategies include firm attachment to prevent mechanical removal, avoidance of phagocytosis, and impairment of phagocytic function by release of toxins or other components that prevent ingestion or intracellular killing of microbes. Some pathogens degrade antibodies or deplete complement components that are important for host defense. Other pathogens alter the vascular supply to tissue, thus creating an environment that restricts defensive resources and impairs antimicrobial activity in the affected area.

When host defenses are significantly inhibited, microbial growth can proceed if nutritional supplies are adequate and the pH, temperature, and oxidation–reduction potential are appropriate. Host control of these parameters is important in host defense. Iron is often a limiting nutrient for microbial growth. The ability to appropriate iron from host iron-binding proteins (transferrin and lactoferrin) is an important factor in microbial virulence. Gastric acidity makes the stomach a harsh environment for many pathogenic bacteria, although in response to acid stress some bacteria express alternative sigma factors that result in transcription of genes whose products help the pathogen survive in an acidic environment (e.g. ***Salmonella*** and **enterohemorrhagic** *E. coli*). The higher body temperature of birds may explain in part their resistance to some infectious diseases (e.g. anthrax and histoplasmosis). Requirements for a reduced oxygen environment allow anaerobic bacteria to multiply in tissues devitalized (i.e. nonoxygenated) as a result of injury, or in which prior or concomitant growth of facultative anaerobic organisms has sufficiently reduced the available oxygen.

Viral Infections

The outcome of any virus–host interaction will depend on various critical factors such as virus–cell interactions, susceptibility of the animal host, route of exposure, mode of virus dissemination, and host resistance. Although most virus-infected animals presented to veterinarians exhibit clinical signs, it is important to recognize that viral infections of animals often result in asymptomatic or subclinical infection. Nor can virulent viruses infect animals that are resistant to them. The potential consequences of virus–animal relationships are listed in Table 1.2.

Table 1.2 Consequences of virus–animal relationships.

No pathogenesis or disease	No disease – replication and transmission with no or minimal pathological changes
Some tissue damage and inflammation	Mild clinical disease with rapid viral clearance and minimal transmission, limited to localized tissues (no dissemination)
Moderate clinical disease	Significant replication and shedding of virus to sustain transmission, some tissue replication, viremia – inflammation associated with some clinical signs (fever, malaise, tissue-specific signs)
Severe clinical disease	Infect host tissues, significant viremia, and shedding – clinical signs associated with tissue damage (respiratory or neurological, for example) or systemic host responses (fever, malaise, muscle pain, and even shock) Some viral infections may be limited to specific tissues with little viremia and no broad cross-tissue dissemination (feline immunodeficiency virus). Manifestations of disease may be the result of a prolonged perturbation of cellular function or cellular loss (immunodeficiency)
Fatal or other serious outcomes	Infection that results in severe disease leading to death from mechanisms described above for severe clinical disease. This could include permanent tissue damage resulting from viral replication or consequent inflammation

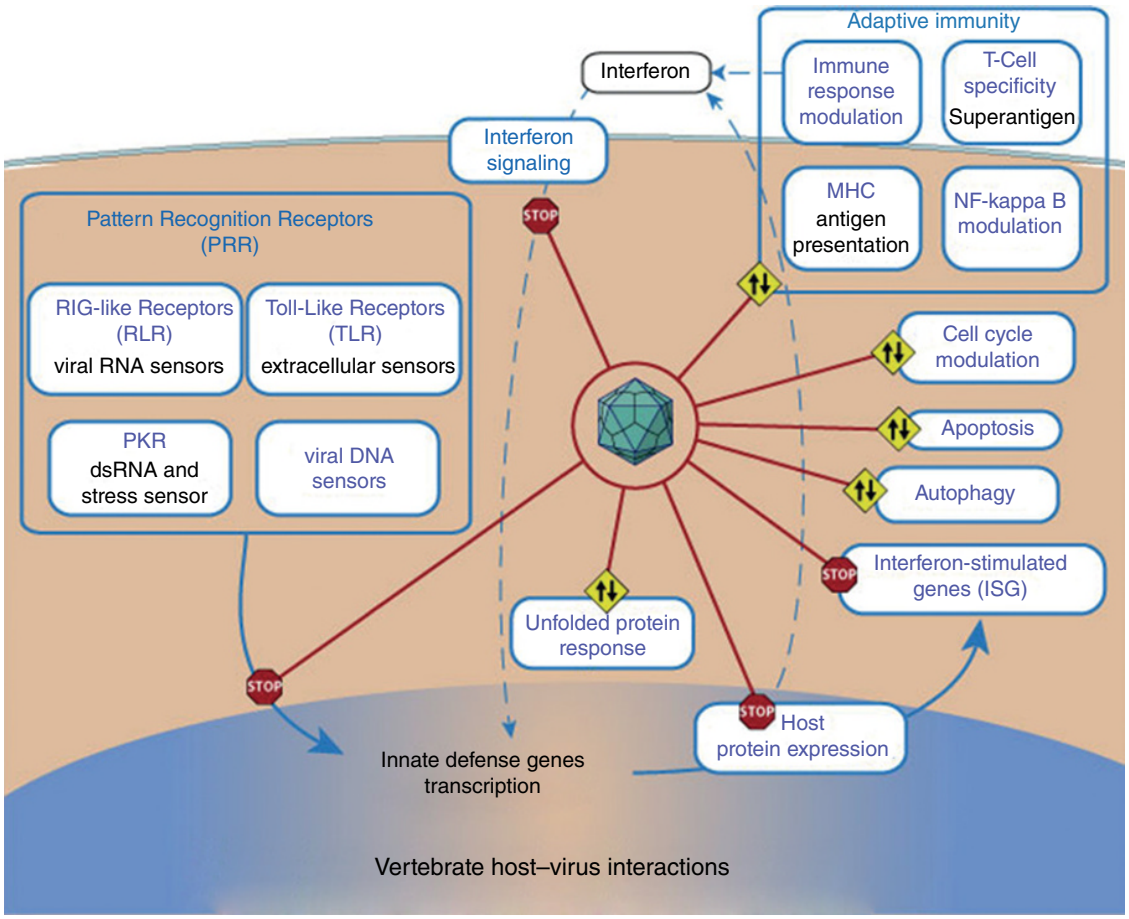

Figure 1.1 Interactions of viruses with host cells. *Source:* Courtesy of Creative Commons Corporation and ViralZone, 2021, https://creativecommons.org/licenses/by/4.0/#; https://viralzone.expasy.org/.

There are several major routes of viral entry into a host: respiratory, alimentary, urogenital, and direct transmission via an insect or animal bite. Successful establishment of viral infection depends on the presence of appropriate cell receptors for viral attachment and internalization, and the physicochemical nature of the viral agent (Figure 1.1). To successfully initiate infection, a virus must survive until a susceptible host is encountered and access is gained to cells in which it can replicate (permissive cells). This requires the virus to overcome the host defense mechanisms at these sites. For example, viruses that infect animals via the alimentary tract are typically resistant to the low pH and potent enzymes that occur in the digestive tract.

Mechanisms of Pathogenesis

Microbial disease manifests itself either as the result of direct damage to host cells and cellular functions by exotoxins or products of microbial growth, or via collateral damage due to host inflammatory or immune reactions that are triggered by the microbe or microbial components (e.g. endotoxin).

Direct Damage

Exotoxins are usually bacterial proteins that are freely excreted into the environment, whereas endotoxin (lipopolysaccharide) is an integral part of the gram-negative bacterial cell membrane that remains attached to the bacterial cell or is released in membrane vesicles. The different characteristics of endotoxins and exotoxins are described in Table 1.3 and Figure 1.2.

Exotoxins are encoded chromosomally, on plasmids or on bacteriophages. These toxins produce injury by destroying the cells in which they replicate or by altering cell function, appearance, and growth characteristics. There are several types of bacterial exotoxins. Some act extracellularly by damaging host cell membranes via enzymatic or

Table 1.3 Exotoxins and endotoxins compared.

Exotoxins	Endotoxins
Often spontaneously diffusible	Cell-bound as part of the cell wall
Proteins or polypeptides	LPS (lipid A is a toxic component)
Produced by gram-positive and gram-negative bacteria	Limited to gram-negative bacteria
Produce a single, pharmacologically specific effect	Produce a range of effects, largely due to host-derived mediators
Each is distinct in structure and reactivity according to its bacterial species of origin	Similar in structure and effect regardless of bacterial species of origin
Lethal in minute amounts (mice = nanograms)	Lethal in larger amounts (mice = micrograms)
Labile to heat, chemicals, and storage	Very stable to heat, chemicals, and storage
Convertible to toxoids (nontoxic, immunogenic toxin-derivatives); elicit antitoxin production	Not readily convertible to toxoids

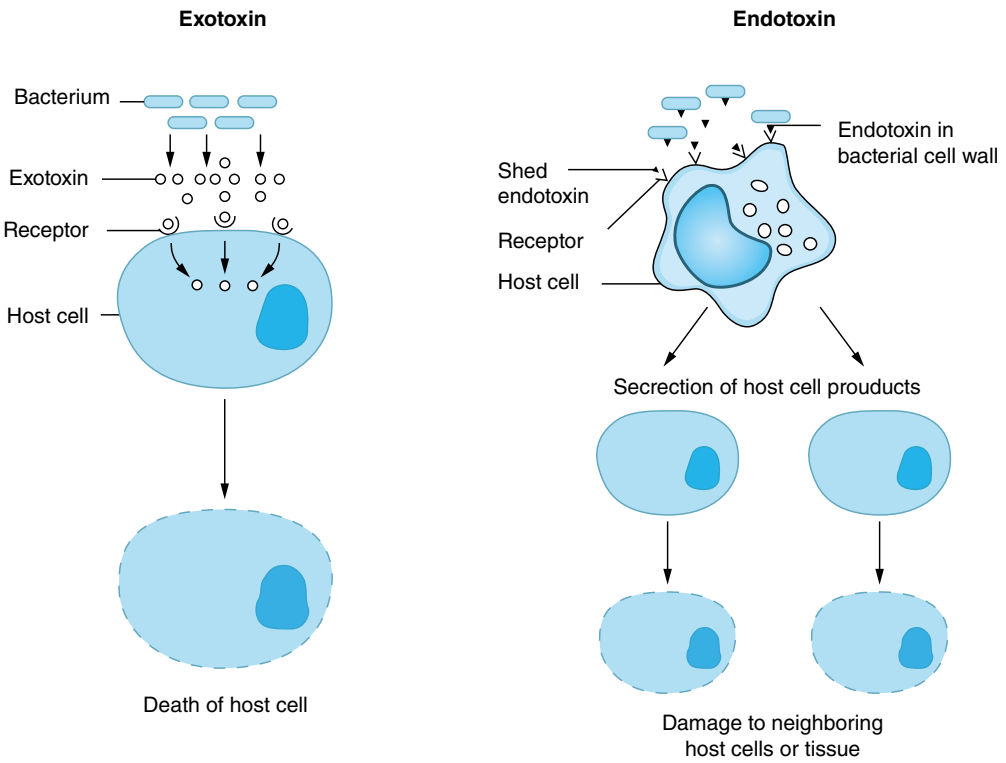

Figure 1.2 A comparison of endotoxins and exotoxins. *Source:* Used courtesy of the Creative Commons and @Read/Study, 2021.

detergent-like mechanisms. Examples of these toxins include bacterial hemolysins, and leucocidins. Some exotoxins act as enzymes that degrade the extracellular matrix (e.g. collagenases and hyaluronidases) and play an ancillary role in facilitating bacterial spread in host tissue. One group of exotoxins consists of proteins or polypeptides that enter cells and enzymatically disrupt intracellular processes. Many, but not all, of these are bifunctional polypeptides that consist of an A fragment with enzymatic activity and a B fragment that is responsible for toxin binding to target cells.

Endotoxins are lipopolysaccharides (LPS) that are part of the gram-negative cell wall and outer membrane. The LPS structure consists of a core polysaccharide, lipid A (which is the toxic moiety) and polysaccharide chains. The latter can act as an adhesin or virulence factor and contain

the somatic (O) antigens recognized by the host immune response. LPS can bind directly to leukocytes, or to LPS-binding protein (a plasma protein), which in turn transfers the LPS to CD14. The CD14–LPS complex interacts with other receptor proteins (e.g. Toll-like receptor 4) on the surface of macrophages and other cells, triggering the release of proinflammatory cytokines and other mediators that elicit the manifestations of endotoxemia. These can include fever, headache, hypotension, leukopenia, thrombocytopenia, intravascular coagulation, inflammation, endothelial damage, hemorrhage, fluid extravasation, and circulatory collapse. Many of these outcomes result from LPS or cytokine stimulating: (i) activation of the complement cascade; and (ii) production of arachidonic acid metabolites (prostaglandins, leukotrienes, and thromboxanes). The clinical signs of endotoxemia closely resemble those of gram-negative septicemias. Although mediated by different bacterial components (lipoproteins) and host receptors (Toll-like receptor 2), similar manifestations can be induced by the cell walls (peptidoglycans) of gram-positive bacteria.

Immune-Mediated Damage

Tissue damage due to immune reactions is considered in detail elsewhere in this volume (see Chapter 67). Innate immune and inflammatory responses are both essential to host defense and can cause substantial tissue damage and loss of function. For example, complement-mediated inflammation can occur in response to endotoxins or to peptidoglycan without preceding sensitization and can result in a vigorous local inflammatory response. Antigen-specific adaptive immune responses contribute to the pathogenesis of many infections, particularly those, such as tuberculosis, that elicit chronic granulomatous infection. Granulomas that form in response to infection with intracellular pathogens such as *M. tuberculosis* are the result of a cell-mediated immune response (Type IV delayed type hypersensitivity) by the host. These cell-mediated immune responses can damage tissue during the original infection, or upon subsequent encounters with the offending microorganisms or its antigens that stimulate T lymphocytes to release cytokines and other effector molecules. Other examples of immune-mediated damage include anemia seen in anaplasmosis, and during infection with the hemotrophic mycoplasmas. These occur as the result of an antibody response to the hemoparasites that targets infected host erythrocytes for phagocytosis and C-mediated hemolysis.

Viral Dissemination within the Infected Host

Viruses cause two basic patterns of infection: localized or generalized (Figure 1.3). In localized infections, viral multiplication and cellular damage remain localized near the site of entry (e.g. the skin or the mucous membranes of the respiratory, gastrointestinal, or genital tract). The infecting virus spreads only to neighboring cells immediately adjacent to the original site of infection. For example, rhinovirus infections of animals are often restricted to the nasal epithelium and do not spread to the lower respiratory tract. Other respiratory viruses, such as parainfluenza and respiratory syncytial viruses, can replicate within the lungs of infected animals, but tissue injury does not extend beyond the respiratory tract. Generalized infections develop through several sequential steps: (i) the virus undergoes primary replication at the site of entry and in regional lymph nodes, (ii) progeny virus spreads through blood (primary viremia) and lymphatics to additional tissues, where (iii) further virus replication takes place, (iv) the virus is disseminated to the other target organs via a secondary viremia, and (v) it multiplies further in these target tissues where it causes cellular degeneration and/or necrosis, tissue injury, and clinical disease.

After the initial viral invasion, there is an asymptomatic incubation period before clinical signs are observed. In generalized viral infections, overt disease begins after the virus is widely disseminated in the body and replicates to significant levels. It is at this stage that the veterinarian typically is first alerted. Canine distemper provides an example of a generalized viral infection of animals. Canine distemper virus initiates infection at the site of entry, and then disseminates through the blood or lymphatic system to produce generalized infection that involves a variety of target organs (Figure 1.4). The sequence of events during the incubation period and clinical signs that occur in individual animals depend on which organ systems are infected by the virus. The virus is disseminated to these organs during the viremic period, in which viral dissemination occurs both via free virus particles in the blood and infected blood cells that serve as carriers to transport the virus to target organs (cell-associated viremia). Cell-associated viremias typically involve blood leukocytes, but some viruses, such as bluetongue virus, hog cholera virus, or parvovirus, can associate with and be disseminated by red blood cells in the infected host. For viruses that infect the central nervous system, viral dissemination can occur by viremia or, in the case of rabies, by centripetal transmission along peripheral nerves.