in turn, some bacteria such as N. gonorrhoeae, vary their pili to escape from the host immune system.

***Virulence of Intracellular Bacteria.*** Bacteria have evolved a variety of mechanisms for entering host cells. Some bacteria use the host immune response to gain entry into macrophages. Opsonization of bacteria with antibodies or the complement protein C3b promotes phagocytosis of bacteria by macrophages. Like many bacteria, *M. tuberculosis* activates the alternative complement pathway, resulting in opsonization with C3b. Once coated with C3b, *M. tuberculosis* binds to the CR3 complement receptor on macrophages, enters the macrophages, and replicates within phagosomes. Gram-negative bacteria use a complex secretion system to enter epithelial cells. This type III secretion system consists of needle-like structures projecting from the bacterial surface that bind to host cells. These proteins then form pores in the host cell membrane and inject bacterial proteins that mediate the rearrangement of the host cell cytoskeleton in a fashion that facilitates bacterial entry. Once inside the host cell, other bacteria such as *Listeria monocytogenes* modify the actin cytoskeleton to promote the direct spreading of the organism to neighboring cells, allowing the bacteria to evade immune effector mechanisms.

After bacteria enter the host cell, their fate (and that of the infected cell) varies greatly depending on the organism. *Shigella* and *E. coli* inhibit host protein synthesis, replicate rapidly, and lyse the host cell within hours. Most bacteria are killed within macrophages when the phagosome fuses with an acidic lysosome to form a phagolysosome, but certain bacteria elude this host defense. For example, *M. tuberculosis* blocks fusion of the lysosome with the phagosome, allowing it to proliferate unchecked within the macrophage. Other bacteria avoid destruction in macrophages by leaving the phagosome and entering the cytoplasm. *L. monocytogenes* produces a pore-forming protein called listeriolysin O and two phospholipases that degrade the phagosome membrane, allowing the bacterium to escape into the cytoplasm.

Facultative intracellular bacteria infect epithelial cells (*Shigella* and enteroinvasive *E. coli*), macrophages (*M. tuberculosis, M. leprae*), or both (*S. typhi*). The growth of bacteria in cells can allow them to escape from certain effector mechanisms of the immune response (e.g., antibodies and complement), and can also facilitate the spread of the bacteria. An example of the latter is the migration of infected macrophages carrying *M. tuberculosis* from the lung to draining lymph nodes and other more distant sites.

***Bacterial Toxins.*** Any bacterial substance that contributes to illness can be considered a toxin. Toxins are classified as *endotoxins*, which are components of the bacterial cell, and *exotoxins*, which are proteins that are secreted by the bacterium.

***Bacterial endotoxin* is a lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria that both stimulates host immune responses and injures the host.** Lipid A, which anchors LPS in the host cell membrane through long-chain fatty acids, has the endotoxin activity of LPS. Lipid A is connected to a conserved core carbohydrate chain, which is attached to a variable carbohydrate chain called the O antigen. The response to lipid A is beneficial in that it activates protective immunity in several ways. It induces the production of important cytokines and chemoattractants (chemokines) by immune cells and increases the expression of costimulatory molecules, which enhance T-lymphocyte activation. However, high levels of endotoxin play a pathogenic role in septic shock, disseminated intravascular coagulation (DIC), and adult respiratory distress syndrome, mainly through induction of excessive levels of cytokines such as TNF, IL-1, and IL-12. LPS binds to the cell-surface receptor CD14, and the complex then binds to Toll-like receptor 4 (TLR4), a pattern recognition receptor that activates cells of the innate immune system.

***Exotoxins* are secreted bacterial proteins that cause cellular injury and disease.** They can be classified into broad categories by their site or mechanism of action. These are briefly described next and discussed in more detail in the specific sections about each type of bacteria.

- *Enzymes.* Bacteria secrete a variety of enzymes (proteases, hyaluronidases, coagulases, fibrinolysins) that act on their respective substrates in vitro, but the role of only a few of these in disease is understood. For example, exfoliative toxins produced by *S. aureus* cause staphylococcal scalded skin syndrome by degrading proteins that hold keratinocytes together, causing the epidermis to detach from the deeper skin.
- *Toxins that alter intracellular signaling or regulatory pathways.* Most of these toxins have an active (A) subunit with enzymatic activity and a binding (B) subunit that binds to receptors on the cell surface and delivers the A subunit into the cell cytoplasm. The effects of these toxins are diverse and depend on the binding specificity of the B domain and the cellular pathways affected by the A domain. A-B toxins are made by many bacteria including *Bacillus anthracis, V. cholerae*, and some strains of *E. coli*.
- *Neurotoxins* produced by *Clostridium botulinum* and *Clostridium tetani* inhibit release of neurotransmitters, resulting in paralysis. These toxins do not kill neurons; instead, the A domains interact specifically with proteins involved in secretion of neurotransmitters at the synaptic junction. Both tetanus and botulism can result in death from respiratory failure due to paralysis of the chest and diaphragm muscles.
- *Superantigens* are bacterial toxins that stimulate very large number of T lymphocytes by binding to conserved portions of the T-cell receptor, leading to massive T-lymphocyte proliferation and cytokine release. The high levels of cytokines can lead to capillary leak and shock. Superantigens made by *S. aureus* and *S. pyogenes* cause toxic shock syndrome (TSS).

## KEY CONCEPTS

### How Microorganisms Cause Disease

- Diseases caused by microbes involve interplay between microbial virulence factors and host responses.
- Infectious agents cause death or dysfunction by directly interacting with the cell.