



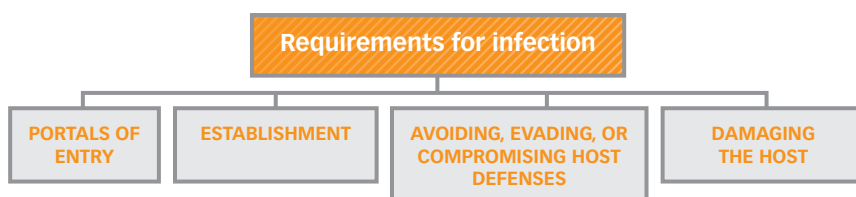
### Why Is This Important?

This chapter introduces you to the mechanisms involved in the infectious disease process. What you learn here will be the foundation for the rest of your studies in microbiology.

### OVERVIEW

This is a very important chapter because it is here that we begin to look at the fundamentals of the infectious disease process. Armed with the concepts from previous chapters, we are well prepared for these discussions about the specifics of what is involved in the infectious disease process. We will then build on this information as we move through future chapters. In this chapter, we examine four of the five requirements necessary for a successful infection, namely portals of entry (getting in), establishment (staying in), defeating the host defenses, and damaging the host.

We will divide our discussions into the following topics:



As we saw in PART I of this book, there are five fundamental requirements for a successful infection. Pathogens must be able to:

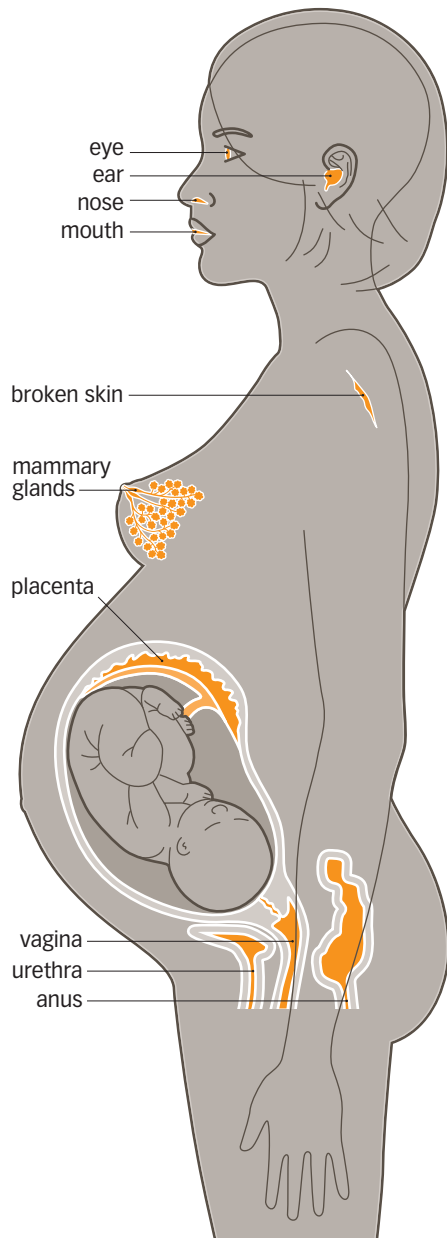
1. Enter the host (get in).
2. Have the ability to remain in a location while the infection gets established. We can call this process *establishment* (staying in), and this can include increasing the number of pathogenic organisms.
3. Avoid, evade, or compromise the host defenses (defeat the host defenses).
4. Damage the host.
5. Exit from the host and survive long enough to be transmitted to another host (transmissibility, covered in Chapter 6).

For pathogens to accomplish this, they use their **virulence factors**. These are the characteristics that the pathogens possess that allow them to thrive and survive in the host's environment. They are also the "weapons" that have a role in how virulent a microbe is and are responsible for many of the symptoms in the host. As we discuss the requirements for a successful infection in this chapter, you will see the important role of these virulence factors in the process.



### What Do I Need to Know?

To get the most out of this chapter, please review the following terms from your previous courses in biology, anatomy, physiology, or chemistry or in previous chapters of this book as indicated in parentheses: cytokine, endocytosis (4), exocytosis (4), electrolyte, lipoprotein (2), lipopolysaccharide (2), lysis, lamina propria, phospholipid (4), Peyer's patches.



**Figure 5.1** Portals of entry

**i Fast Fact**

In total, there are about 400 square meters of mucous membrane surface area in the human body. That represents a lot of potential entry points.

## PORTALS OF ENTRY (GETTING IN)

The entry of pathogens is a primary requirement for infection and it is relatively easy in humans because so much of the body is open to the outside world (**Figure 5.1**). Any point at which organisms can enter the body is called a **portal of entry**, and we can divide these portals into three categories: mucous membranes, skin, and parenteral routes (**Table 5.1**). The skin and mucous membranes are in direct contact with the exterior environment and are therefore in close proximity to potential pathogens. In contrast, pathogens that enter the body via the parenteral route take advantage of breaks in the body's barriers to gain access.

### Mucous Membranes

Recall from your studies of anatomy that mucous membranes are located in areas of the body that are adjacent to the outside world. These membranes are found in the respiratory tract, the gastrointestinal tract, and the genitourinary tract.

Portal of Entry	Pathogen	Disease
Respiratory-tract mucous membranes	<i>Streptococcus</i> species	Pneumonia
	<i>Mycobacterium tuberculosis</i>	Tuberculosis
	<i>Bordetella pertussis</i>	Whooping cough
	Influenza virus	Influenza
	Measles virus	Measles (rubeola)
	Rubella virus	German measles (rubella)
	Varicella-zoster virus	Chickenpox
Gastrointestinal-tract mucous membranes	<i>Shigella</i> species	Shigellosis (bacillary dysentery)
	<i>Escherichia coli</i>	Enterohemorrhagic disease
	<i>Vibrio cholerae</i>	Cholera
	<i>Salmonella enterica</i>	Salmonellosis
	<i>Salmonella typhi</i>	Typhoid fever
	Hepatitis A virus	Hepatitis A
	Mumps virus	Mumps
Genitourinary-tract mucous membranes	<i>Neisseria gonorrhoeae</i>	Gonorrhea
	<i>Treponema pallidum</i>	Syphilis
	<i>Chlamydia trachomatis</i>	Nongonococcal urethritis
	Herpes simplex virus	Herpes
	Human immunodeficiency virus	Acquired immunodeficiency syndrome
Skin or parenteral route	<i>Clostridium perfringens</i>	Gas gangrene
	<i>Clostridium tetani</i>	Tetanus
	<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever
	Hepatitis B and C	Hepatitis
	Rabies virus	Rabies
	<i>Plasmodium</i> species	Malaria

**Table 5.1** Portals of Entry for Some Common Pathogens

You can think of the enormous surface area of the mucous membranes as a border, analogous to the border between two nations. Fortunately, as we will see in Chapter 15, the body has a variety of powerful border defenses that prevent entry. Consequently, even though the surfaces of the respiratory, gastrointestinal, and genitourinary tracts are in contact with potential pathogens, the surfaces have means of protecting the body against the entry of microorganisms.

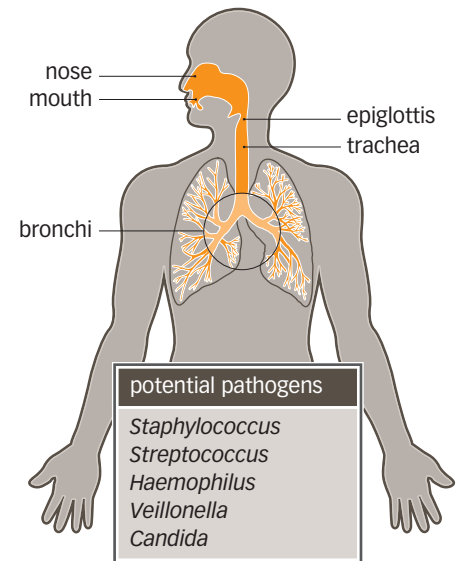
### The Respiratory Tract

Of all of the portals of entry, this is probably the most favorable to pathogens (Figure 5.2). We live in a cloud of potentially dangerous microbial pathogens, and the respiratory tract facilitates entry through breathing. Organisms can be found on droplets of moisture in the air and even on dust particles, and many diseases, such as colds, pneumonia, tuberculosis, influenza, **measles**, and even **smallpox**, use this portal of entry. As we will see later in this chapter, the respiratory tract is also a very productive portal of exit that can be used to transmit pathogens through coughing or sneezing. (A **portal of exit** is any point at which microorganisms can leave the body.)

### The Gastrointestinal Tract

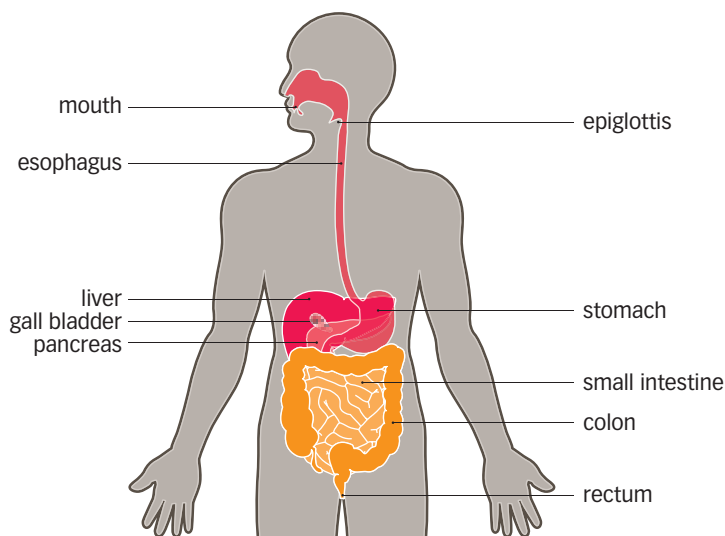
This system is also open to the outside world, and organisms can enter the body via the foods and liquids we eat and drink. The gastrointestinal tract has many protective barriers against pathogens, the most obvious of which is the production of stomach acid and bile. These substances are required for normal digestion but produce hostile environments that limit the survival of most pathogens. Still, there are many organisms that not only use this portal of entry but actually prefer or require it. For example, the polio virus uses the gastrointestinal tract as a required part of its infectious cycle. In addition, the tract is a preferred entry point for hepatitis A virus, the parasite *Giardia*, the bacterium *Vibrio cholerae*, and organisms that cause **dysentery** and typhoid fever (Figure 5.3).

One of the more interesting pathogens that use this portal of entry is *Helicobacter pylori*. This organism is carried in the gastric mucosa of one out of every two people in the world, and infection with this organism is a known risk factor for the development of gastroduodenal ulcers. For many years, it was thought that the acidity of the stomach (about pH 1.0) would preclude bacterial survival, but *H. pylori* has consistently been shown to



**Figure 5.2** Mucous membranes of the upper respiratory tract are portals of entry for potential pathogens.

The upper respiratory tract is the body's most accessible portal of entry because organisms are brought in through the breathing process.



**Figure 5.3** Mucous membranes of the gastrointestinal tract are portals of entry to the body.

Microorganisms enter with food or water, but much of this system is an inhospitable environment for them. This is a preferred portal of entry for some pathogens such as *Salmonella*.

upper digestive tract	lower digestive tract
potential pathogens	potential pathogens
<i>Haemophilus</i> <i>Actinomyces</i> <i>Treponema</i> <i>Neisseria</i> <i>Corynebacterium</i> <i>Entamoeba</i> <i>Trichomonas</i>	<i>Escherichia</i> <i>Lactobacillus</i> <i>Clostridium</i> <i>Enterococcus</i> <i>Proteus</i> <i>Shigella</i> <i>Candida</i> <i>Entamoeba</i> <i>Trichomonas</i>

be associated with gastroduodenal lesions. It turns out that *Helicobacter* can produce a relatively alkaline atmosphere around itself that protects it during its journey in the stomach by neutralizing the acidic pH found there. The organism eventually makes its way to the mucus that lines the wall of the stomach and duodenum of the small intestine. Nestled in this mucus, it is protected and can begin the process of infection that results in the destruction of tissue and the formation of an ulcer.

The gastrointestinal tract is also a leading portal of exit for pathogens in feces. In fact, we will see throughout our discussions of infectious disease that the **fecal-oral route of contamination** has a major role in many infections, especially with Gram-negative bacteria, viruses, protozoa, and other parasites.

### The Genitourinary Tract

The urinary and reproductive tracts are also open to the outside world, but unlike the respiratory and gastrointestinal tracts, they are more complicated with respect to entry.

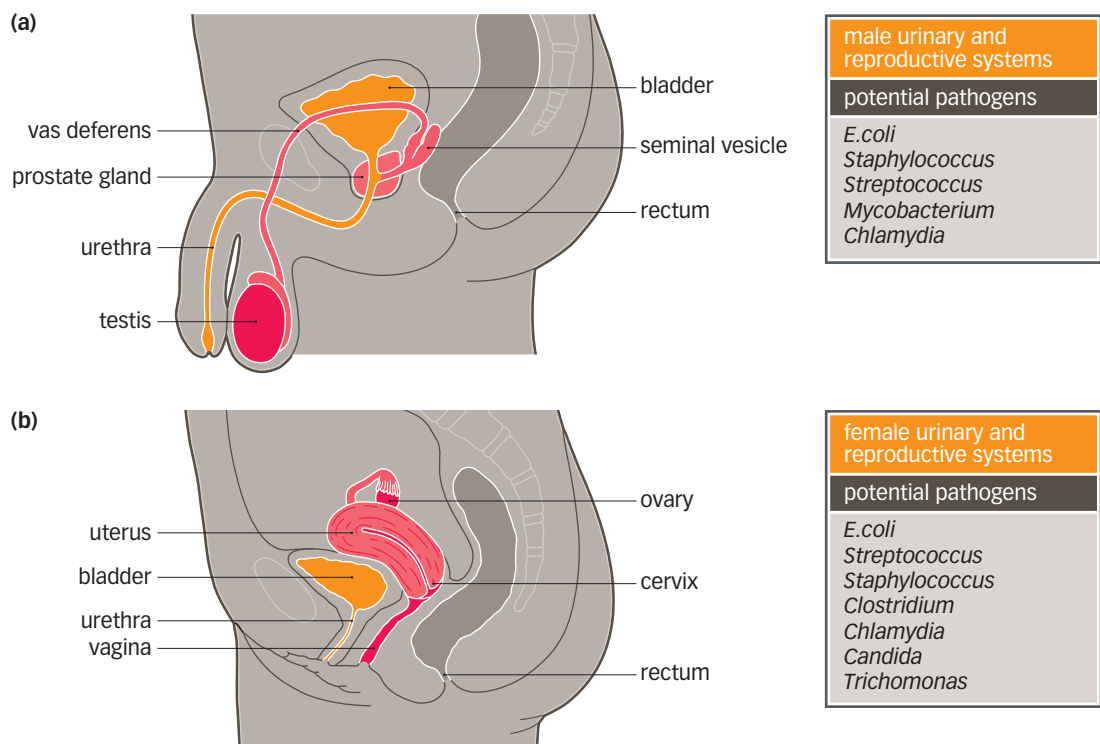
Urinary tract infections are more common in women than in men because of the anatomical relationship between the anus and urethra, which is much closer in women than in men (**Figure 5.4**). Because fecal material contains bacteria, it is easy for these organisms to find their way to the urinary tract.

Diseases of the reproductive tract are usually sexually transmitted and occur as a result of either abrasions or tiny tears in the tissues that routinely occur during sexual activity. Once the mucous membrane barrier is broken, pathogens gain entry. Conditions such as syphilis, gonorrhea, chlamydia, herpes, **genital warts**, and HIV infections are caused by pathogens that use this portal of entry. The genitourinary tract can also be used as a portal of exit through which these infections can be transmitted. Fortunately, this route is well protected by host defenses.

### Fast Fact

Urinary tract infections are easily treated, and no serious damage is done unless the pathogens find a way up into the bladder or the kidneys.

**Figure 5.4 Genitourinary portals of infection.** Panel **a**: The male urinary and reproductive tract. Panel **b**: The female reproductive and urinary tract. In both sexes, both tracts are portals of entry for pathogens. Urinary tract infections occur more frequently in females than in males because of the anatomical relationship between the anus and the urethra.



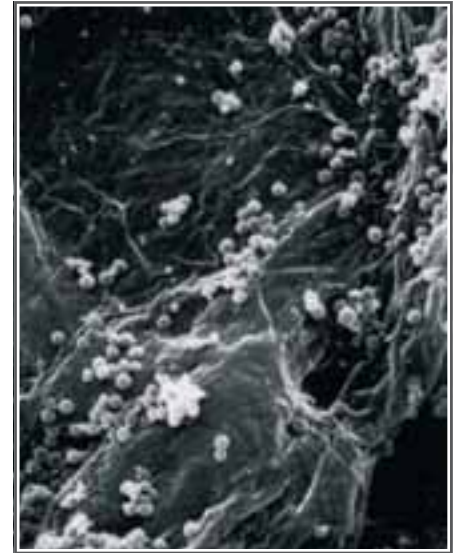
## Skin

The skin is the largest organ in the body, and like the mucous membranes it has a vast surface area through which microorganisms may enter the body. However, unlike the case with the mucous membranes, the association between the skin and microorganisms does not depend on their being taken in through breathing, eating, or sexual activity. The microorganisms are already there. In fact, the skin is literally covered with many types of microorganism and easily accessible to many other types, including pathogens. Fortunately, the skin is impenetrable to most microorganisms. In fact, many bacteria, fungi, and some parasites, that live on the skin are completely harmless to the host (**Figure 5.5**). To initiate an infection, these organisms must find an opening, such as a hair follicle, a perspiration duct, or a break in the skin, so as to gain entry. We will see that these potential entry points are very well guarded.

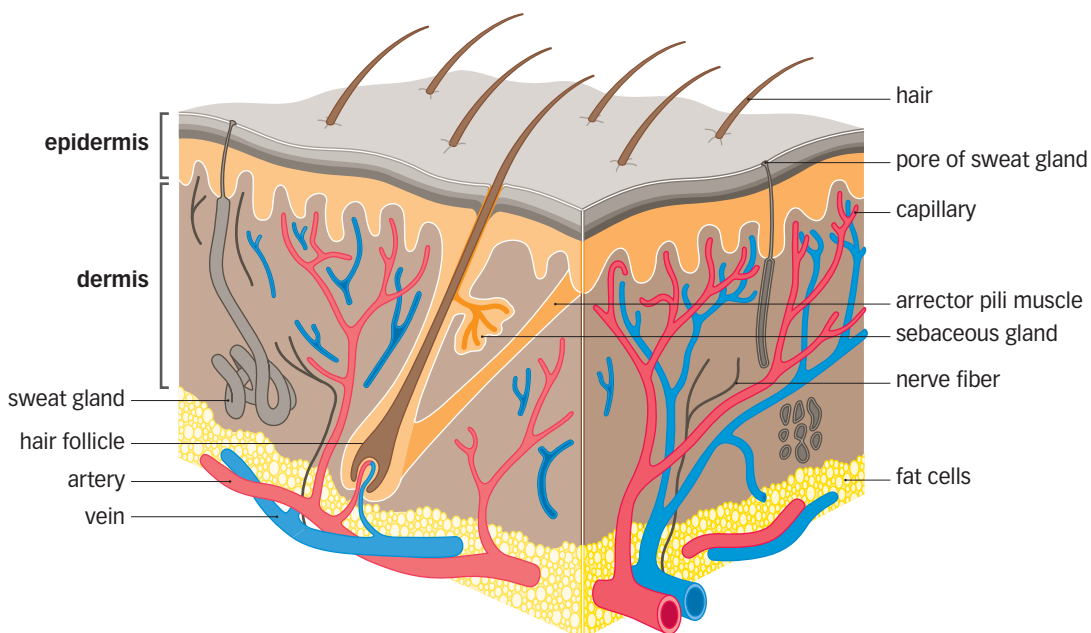
## The Parenteral Route

Movement of organisms past the barrier of the skin requires a break in the barrier, and the portal of entry referred to as the **parenteral route** depends on such breaks. Things such as injections, which are routinely used in clinical applications, can easily become parenteral portals of entry any time that microorganisms are present in close proximity to the site of injection. Entry can also occur via insect bites (referred to as **vector transmission**), and many organisms, such as *Plasmodium* (the causative agent of **malaria**), use this as a way to enter the host.

Obviously, any cut or wound is going to allow the entry of skin-dwelling organisms, but the extent of the trauma can also have a role in the severity of the subsequent infection. Recall that the skin is made up of two basic layers, the epidermis and the dermis (**Figure 5.6**). Because the epidermis is made up of dead and dying cells, there is no access of blood to this



**Figure 5.5** The skin and conjunctiva of the eye are in constant contact with microorganisms but present an impenetrable barrier to entry. These barriers must be compromised in some way in order for organism to enter. This scanning electron micrograph shows some of the microorganisms that inhabit the skin.



**Figure 5.6** A diagrammatic representation of a cross section of the skin. Pathogens that gain access to the epidermis usually result in localized infections, whereas those that enter the dermis can cause systemic problems because of the availability of blood in this layer of the skin.

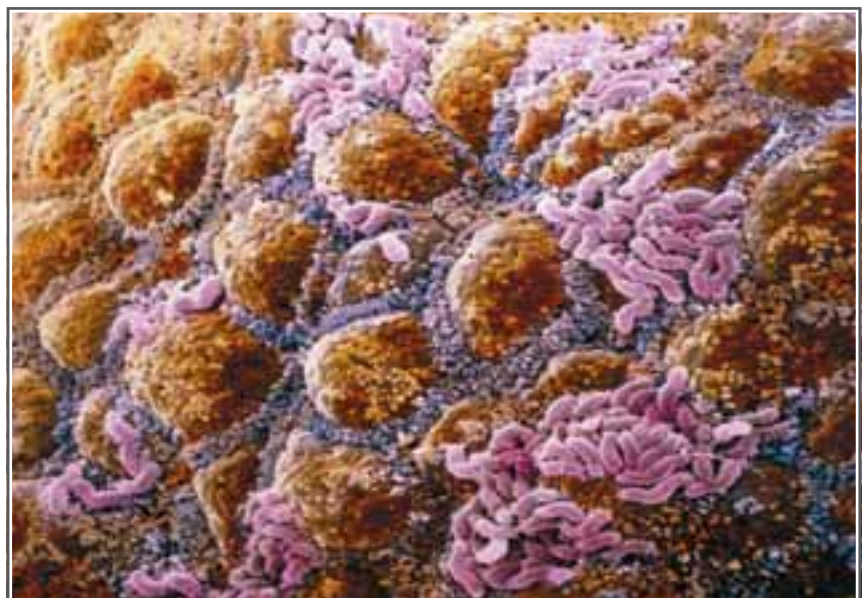
layer. Therefore, cuts or wounds limited to this layer are less likely to spread beyond the site of entry. In contrast, the dermis is associated with blood vessels, and cuts or wounds that involve this layer or go deeper are far more likely to cause more serious systemic infections. This is even more apparent when we look at surgical procedures, in which contaminating organisms can gain access deep into internal tissues.

Some organisms have *preferred* portals of entry, and only entry through the preferred portals will result in infection. For example, *Salmonella enterica* serovar Typhi (also known as *Salmonella typhi*) must be swallowed if it is to cause intestinal infections, whereas streptococci must be inhaled to cause pneumonia. However, many organisms can cause infection no matter what entry point is used. A case in point is *Yersinia pestis*, the organism that causes bubonic plague. This organism uses multiple entry points, and in the Middle Ages it wiped out one-third to one-half of the population of Europe.

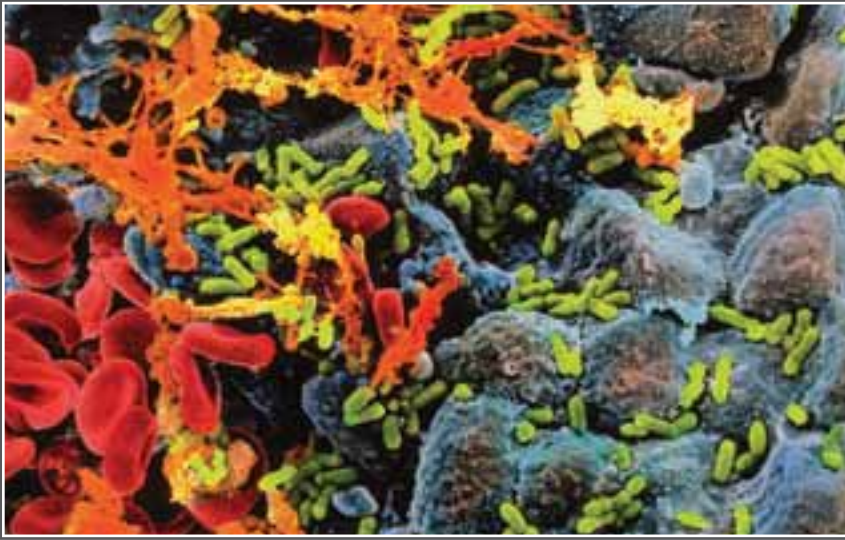
### ESTABLISHMENT (STAYING IN)

Entry into the host is just the beginning of the problems most pathogens face. After entry, a pathogen must find a way to stay in the host if it is to establish the focus of the infection. This task is very difficult for a variety of reasons. For instance, there can be physical obstacles to overcome. Let's use *Neisseria gonorrhoeae* as an example. If, after gaining access to the genitourinary tract, this microorganism does not have a way of adhering to the tissue, it might be flushed back out during urination. On top of this is the vast array of defenses the body has in place to destroy the organism.

In Chapter 9 we will look at the anatomical structures of bacteria and see how these structures can have a role in clinical pathogenesis. During these discussions, we will see that organisms such as *Streptococcus pneumoniae* are not infectious without a surrounding capsule that allows them to adhere to the body's tissue and inhibit the host defense. In point of fact, almost all pathogens have some means of attachment. Some Gram-negative organisms — for instance, *Escherichia coli* — use structures called **fimbriae** to attach to certain receptors on cells of the small intestine, colon, and bladder (**Figures 5.7, 5.8, and 5.9**).

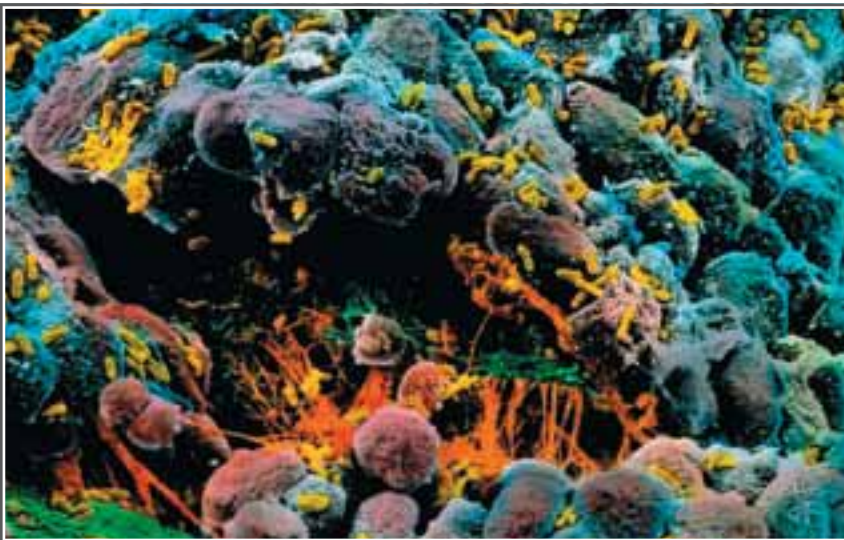


**Figure 5.7** A false color scanning electron micrograph of the surface of the colon mucosa with clusters of bacteria (possibly *E. coli*) attached.



**Figure 5.8** A scanning electron micrograph of bacteria (colored green) adhering to the surface of cells in the colon.

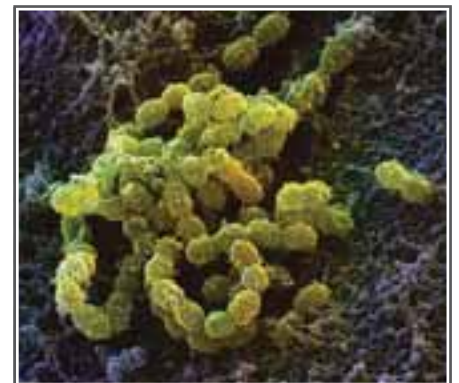
In many cases, pathogens use molecules called **adhesins**, which are glycolipids or lipoproteins located on the pathogen surface, as a means of adhering to tissue (**Table 5.2**). For example, *N. gonorrhoeae* can use fimbriae coated with adhesins to adhere to tissue in the genitourinary tract. Pathogens can also take advantage of “sticky” glycoproteins found on the surface of host cells.



**Figure 5.9** A colorized scanning electron micrograph of cells of the human bladder infected with bacteria. Rod shaped *E. coli* (colored yellow) are seen attached to the epithelial cells of the bladder (colored blue). Note the purple colored cells which have swelled and developed a rough surface due to this chronic bladder infection.

Let’s look at a good example of adherence. The organism *Streptococcus mutans* has for a long time been accused of causing tooth decay. In fact, this is not strictly true because tooth decay actually starts with fluids produced by your oral tissues. These fluids form a **pellicle**, which is a protein film that coats your teeth. *S. mutans* adheres to this pellicle (**Figure 5.10**) and begins to produce the enzyme glycosyltransferase. The problem is

**Figure 5.10** A colorized scanning electron micrograph of dental plaque. The yellow-green structures are *Streptococcus mutans* adhering to a biofilm that covers the teeth. Other organisms adhere to *S. mutans* and cause the development of a biofilm. The organisms in this biofilm produce the enzymes that can cause destruction of the tooth, resulting in the formation of a cavity.



Location	Bacterium	Disease	Mechanism of Adherence
Upper respiratory tract	<i>Mycoplasma pneumoniae</i>	Atypical pneumonia	Cell surface adhesion molecules bind to receptors on cells lining respiratory tract
	<i>Streptococcus pneumoniae</i>	Pneumonia	Adhesion molecules attach to carbohydrates on respiratory cells
	<i>Neisseria meningitidis</i>	Meningitis	Adhesion molecules on bacterial cell attach to respiratory cells
Genitourinary tract	<i>Treponema pallidum</i>	Syphilis	Bacterial proteins attach to cells in reproductive tract
	<i>Neisseria gonorrhoeae</i>	Gonorrhea	Adhesion molecules on bacterium attach to cells in reproductive tract
Gastrointestinal tract	<i>Shigella</i> species	Dysentery	Mechanism not known
	<i>Escherichia coli</i>	Diarrhea	Adhesin molecules on bacterial pili attach to gastrointestinal cells
	<i>Vibrio cholerae</i>	Cholera	Adhesin molecules on bacterial flagella attach to gastrointestinal cells

**Table 5.2 Adherence Factors Associated with Infection**



**Figure 5.11** The spirochete *Treponema pallidum* “corkscrewing” into tissue.

**i Fast Fact**

Drastic increases in pathogen numbers could be a cause for worry except for the fact that humans have developed tremendous defense mechanisms. Consequently, even though a pathogen could potentially proliferate from a single cell to  $10^{21}$  cells in 24 hours, each antibody-secreting plasma cell in the human immune system can produce antibodies against that pathogen at the rate of 2,000 antibody molecules *per second*. More importantly there can be millions of plasma cells!

exacerbated when other organisms adhere to *S. mutans*, forming a bio-film, which is essentially a living coating on the teeth. This combination of organisms and the enzymes they produce causes the destruction of the tooth enamel, resulting in the formation of a cavity. The plaque the dentist removes from your teeth is made up of this complex of organisms. When you consider how hard the dentist has to work to pry this plaque from your teeth, you get a good idea of “establishment.”

Some organisms, such as *Treponema pallidum* (which causes syphilis), avoid the need for protracted periods of adherence by boring into the tissues (**Figure 5.11**).

### Increasing the Numbers

For pathogens, there is safety and success (that is, infectivity) in numbers. In fact, the doubling time for some bacteria can be as little as 20 minutes. This extremely high reproductive rate requires that the growth environment be satisfactory, and for most pathogens the tissues and fluids of the human body are an ideal environment. So the number of organisms required for successful infection can easily be achieved.

There is considerable variability among organisms with regard to the number required for success, and we can run specific experiments to establish the criteria for virulence for any given pathogen. The **lethal dose 50% (LD<sub>50</sub>)** is the number of organisms required to kill 50% of the hosts, and the **infectious dose 50% (ID<sub>50</sub>)** is the number of organisms required for 50% of the population to show signs of infection. Pathogens having the lowest LD<sub>50</sub> and ID<sub>50</sub> values are the most virulent. Using these types of information, we can categorize organisms according to virulence, as shown in **Figure 5.12**.

It is important to remember that bacteria divide by **binary fission** (one bacterium splits into two) and that a pathogen that has a low LD<sub>50</sub> and a short doubling time could be extraordinarily dangerous, with the rapid increase in organisms quickly overwhelming a patient. Fortunately, attacking only rapidly growing bacteria is the way in which many

**Figure 5.12 Degree of virulence attributed to different pathogens.**

This type of appraisal can be made after determining the LD<sub>50</sub> and ID<sub>50</sub> of the pathogens. Remember, the lower the LD<sub>50</sub>, the more virulent the pathogen.

antibiotics work, thereby preventing negative outcomes from infection. Unfortunately, this story is changing, as we will see when we discuss the rapidly expanding resistance to antibiotics in Chapter 20.

In viral infections, the number requirement is easier to understand. A **lytic virus** is defined as one that functions by filling a host cell with viral particles called **virions** until the host cell bursts open and pours virions into the intercellular fluid. These new virions locate new host cells, and the process is repeated until there are no more host cells available. Infection with HIV is a good example. As the infection continues, the host white blood cells known as T4 lymphocytes, which are the viral targets, simply disappear (along with immune capability).

### AVOIDING, EVADING, OR COMPROMISING HOST DEFENSES (DEFEAT THE HOST DEFENSES)

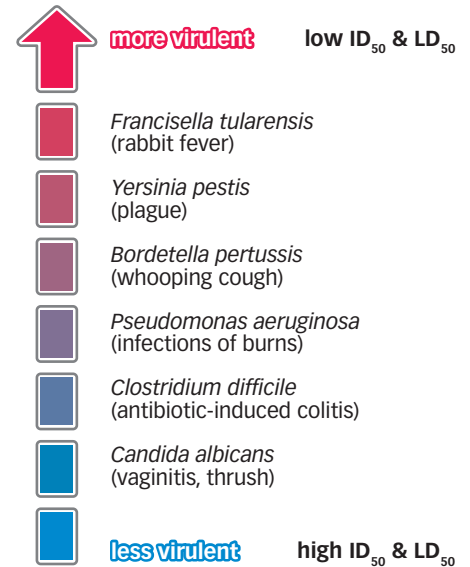
If a pathogen has managed to get into a host, stay in, and rapidly increase its numbers, it is on the way to causing a successful infection. Unfortunately for the pathogen, these steps are usually not enough because there are many ways in which the host can defend itself. Thus, the pathogen has to deal with the host's defenses. There are two basic ways in which this is accomplished; one involves the structure of the pathogen cells, which is a built-in (passive) defense, and the other involves attacking the host's defenses (an active defense).

The main structural defenses of pathogenic bacteria are capsules and cell wall components. In fact, as we noted earlier, encapsulation is required for some organisms to become virulent. For example, unless they are encapsulated, *S. pneumoniae* will not cause pneumonia and *Klebsiella pneumoniae* will not cause Gram-negative bacterial pneumonia. Other bacteria that are virulent only when encapsulated are *Haemophilus influenzae*, *Bacillus anthracis*, and *Yersinia pestis*.

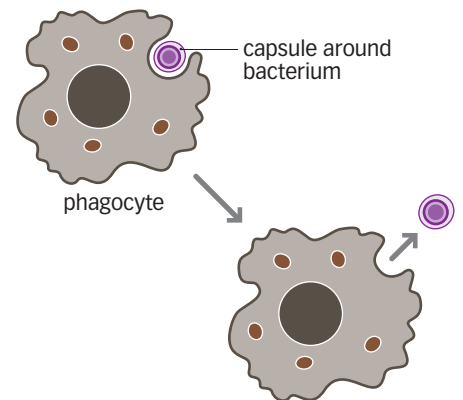
#### Capsule and Cell Wall (Passive) Defenses

The bacterial capsule protects against phagocytosis. In humans, a first line of defense for the innate immune response is **phagocytosis**. In this process, cells known as **phagocytes** ingest pathogens and then destroy them. Pathogens can encapsulate themselves, covering their entire surface in a slimy capsule, which protects against phagocytosis (**Figure 5.13**). The capsular material seems to prevent a phagocyte from adhering to the surface of the bacterium. This adherence is required for the phagocyte to develop *pseudopodia*, "feet" that then surround the organism.

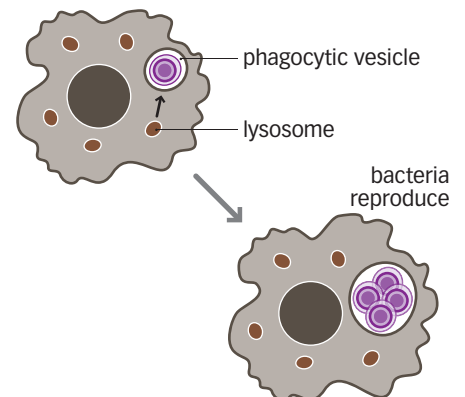
You might think that capsule protection would be all that the pathogen required to overcome the host defense, but that is not quite true. As discussed in Chapter 16, the host can use the adaptive immune response



(a) phagocytosis blocked by capsule



(b) incomplete phagocytosis



**Figure 5.13 A diagrammatic representation of the inhibition of phagocytosis by an encapsulated bacterium.** Encapsulation is a defense mechanism that pathogens have against the defenses of the host. Panel **a**: The capsule keeps the surface of the engulfing phagocyte from sticking to the bacterium, and the bacterium goes free. Panel **b**: Some bacteria not only resist being phagocytosed, but can even multiply once inside the phagocyte.

to produce antibodies against the capsule. When the antibody molecules bind to the capsule (a process known as **opsonization**, which we will discuss in detail in Chapter 16), they attract phagocytic cells that use the antibody molecules as bridges to adhere to the organism and phagocytose it.

A second structural defense available to bacteria is the bacterial cell wall. In Chapter 9, we will see that this wall is a complex structure that protects the bacteria from environmental pressure. The components of the wall can help to increase virulence by defending against host defenses. For instance, *Streptococcus pyogenes* incorporates **M proteins** into its cell wall. These proteins increase the virulence of this pathogen by increasing adherence to host target cells and by making the pathogen resistant to heat and to acidic environments. In addition, M proteins also inhibit phagocytosis and are intimately involved in the condition known as *toxic shock*. Fortunately, the host's immune response can provide antibodies and also fragments of complement proteins that opsonize these bacteria.

Another structural protection is seen in *Mycobacterium tuberculosis*, in which the cell wall is infused with **mycolic acid**, a waxy substance that inhibits phagocytosis and protects the bacterium against antiseptics, disinfectants, and antibiotics.

### Enzyme (Active) Defenses

Capsules and cell wall components are passive measures used to defeat the host defenses. Bacteria also use active defenses against a host by producing extracellular enzymes that enable the infection to spread, and by killing off host defensive cells. The following enzymes are useful against the host defenses.

**Leukocidins** are enzymes that destroy white blood cells in the host. White blood cells are an important part of both the innate and the adaptive host defense systems. Two types of white blood cell are neutrophils and macrophages, which are powerful phagocytic cells. In addition, the white blood cells known as lymphocytes, which are responsible for the adaptive immune response to infection, are destroyed by leukocidins. Leukocidins are produced by staphylococcal and streptococcal pathogens, and it is easy to see how the ability to kill off host defenders can make these organisms dangerous.

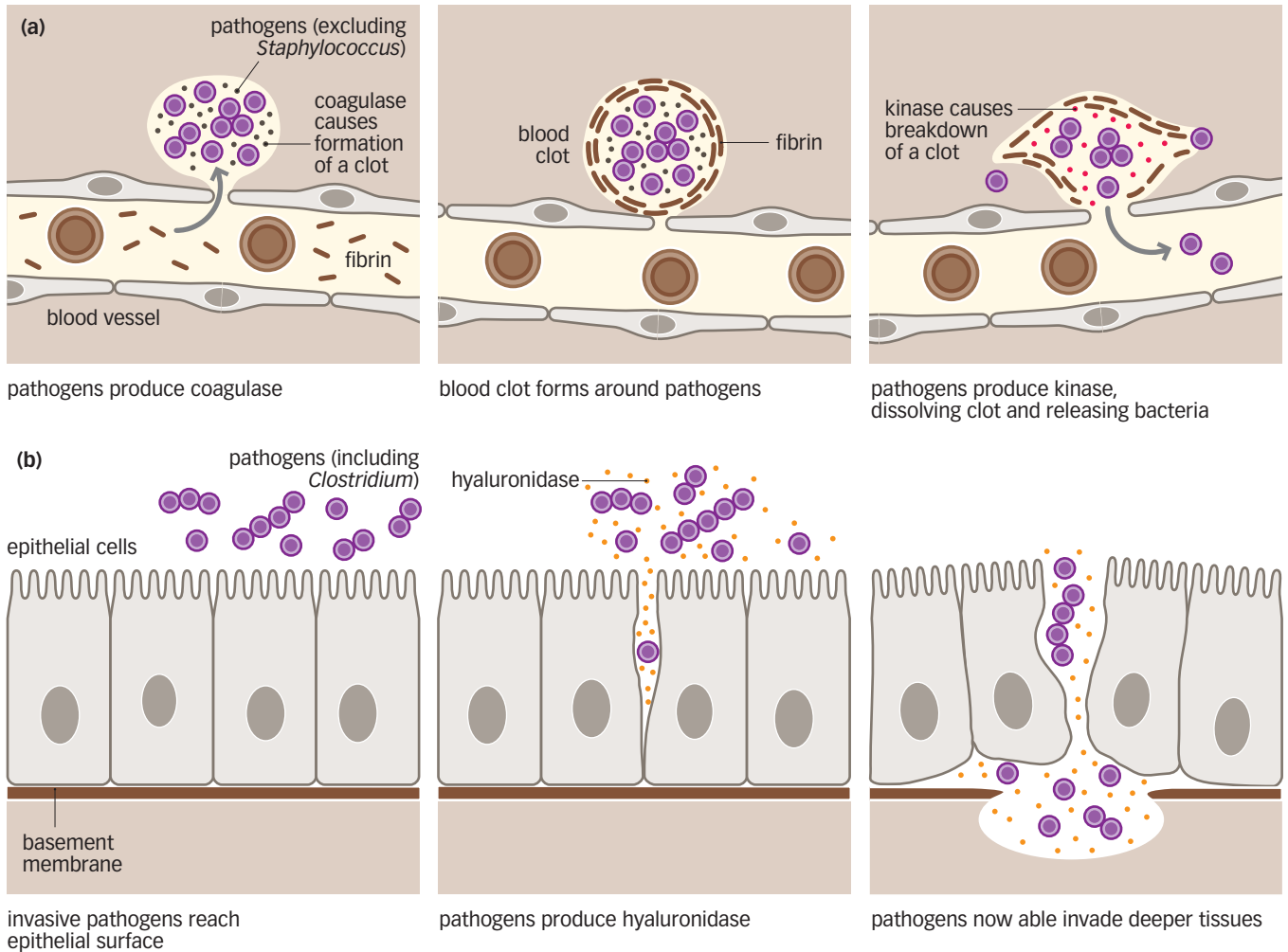
**Hemolysins** are membrane-damaging toxins that disrupt the plasma membrane of host cells and cause the cells to lyse. These toxins can damage the plasma membrane of both red blood cells and white blood cells and are produced by a variety of bacteria, including staphylococcal species, *Clostridium perfringens* (which causes **gas gangrene**), and streptococcal species. Hemolysin produced by streptococcal bacteria is referred to as streptolysin and can be divided into different groups, such as group A and group O. The various groups of streptolysin differ from one another in the type of cell destruction that they cause. For example, streptolysin O is associated with  $\beta$ -hemolysis (complete destruction) of red blood cells.



#### Fast Fact

Knowledge about streptococcal bacteria and their kinase enzymes has saved the lives of many cardiac patients! Scientists have been able to make use of streptococcal bacteria in the lab to produce these enzymes, which are then used as a medical treatment to destroy blood clots.

Coagulase (**Figure 5.14a**) is a pathogen-produced enzyme that causes fibrin clots to form in the blood of a host. Clot formation can be used by both host and pathogen during an infection. The host can use clotting as part of the defense against infection. This clotting occurs in blood vessels around the site of the infection, thereby closing in the pathogens and preventing the spread of the infection. An example of bacterial “walling off” is a **boil** resulting from a localized staphylococcal infection. Here the organism will wall itself off to avoid the host defenses.



**Figure 5.14** Some of the enzymes produced by pathogenic bacteria. Panel **a**: Pathogens can wall themselves off from host defenses using coagulase but can also use kinase to dissolve clots. Panel **b**: The enzyme hyaluronidase allows pathogens to invade deep tissues.

Kinases (**Figure 5.14a**) are enzymes that break down fibrin and dissolve clots. These enzymes can be used by a pathogen to overcome attempts by the host to wall off the infection, thereby ensuring its spread. Staphylokinase is produced by staphylococcal species, and streptokinase is produced by streptococcal species.

Hyaluronidase and collagenase are enzymes that break down connective tissue and collagen in a host, thereby allowing infections to spread (**Figure 5.14b**). Both are active, for instance, in the infection gas gangrene (caused by *C. perfringens*), with the result that the infection is usually widespread and usually involves the destruction of connective tissue.

The process of spreading out is fundamental for the increased virulence of many pathogens. Group A streptococci are a good example. These organisms do not infect any mammals other than humans. They use enzymes as described above to inhibit the clotting machinery or to break down clots formed by the host, allowing the pathogens to spread. There may be a genetic predisposition in humans that has a role in whether streptococcal infections are minor, such as strep throat, or major, such as **necrotizing fasciitis** (flesh-eating; **Figure 5.15**).



**Figure 5.15** A patient with necrotizing fasciitis. This infection is caused by *Streptococcus pyogenes*.

There is one final tactic that pathogens use to defend themselves. They hide! Pathogens can use any of the tactics described above, but in the long run the host's innate and adaptive immune response will catch up with them. Therefore, being able to get *inside* a host cell, where the immune response cannot detect them, is the best possible defense. This is easy for viral pathogens because they are by definition **obligate** intracellular parasites. (*Obligate* means able to survive in only one environment, and for viruses that one environment is inside a host cell.) Bacteria, in contrast, have a harder time getting into a host cell, and so they let the host cell do most of the work by usurping the cell cytoskeleton.

Recall from Chapter 4 that the eukaryotic cell has a variety of fibers — microfilaments, intermediate filaments, and microtubules — that are part of the cellular cytoskeleton and are responsible for cellular support and intracellular movement. Bacteria use these filaments and tubules to penetrate and move around inside the infected cell. As an example, let's look at *Salmonella*. When this pathogen makes contact with a host cell, the contact causes the plasma membrane of the host cell to change its configuration. *Salmonella* produces a molecule called **invasin** that can change the structure of actin filaments in the cytoskeleton. The change in these filaments in turn moves the bacterium into the cell. It gets even better for the pathogen once inside the cell, because now it can use the cell's actin filaments to move from place to place inside the cell. The pathogen can also use a host cell molecule called **cadherin** to move from one cell to another without ever exposing itself to the host's immune defenses searching for it. We will see this mechanism again during our discussion of infections of the digestive tract.



### Keep in Mind

- There are five requirements for a successful infection: get in, stay in, defeat the host defenses, damage the host, and be transmissible.
- Places at which pathogens enter the body are called portals of entry.
- The major portals of entry are the mucous membranes, the skin, and parenteral routes.
- Mucous membrane portals of entry are associated with the respiratory, digestive, and genitourinary tracts of the body.
- Establishment (the requirement of staying in) can be accomplished using adhesion molecules, which are glycolipids or lipoproteins. In addition, some pathogens take advantage of structures such as fimbriae to adhere to tissues.
- Criteria for virulence for a given pathogen can be gauged by the  $ID_{50}$  and  $LD_{50}$  of that organism.
- Pathogens can defeat a host's defenses in two ways: passively (by using structures such as the capsule) and actively (by attacking the host defense directly through the production of enzymes).

### DAMAGING THE HOST

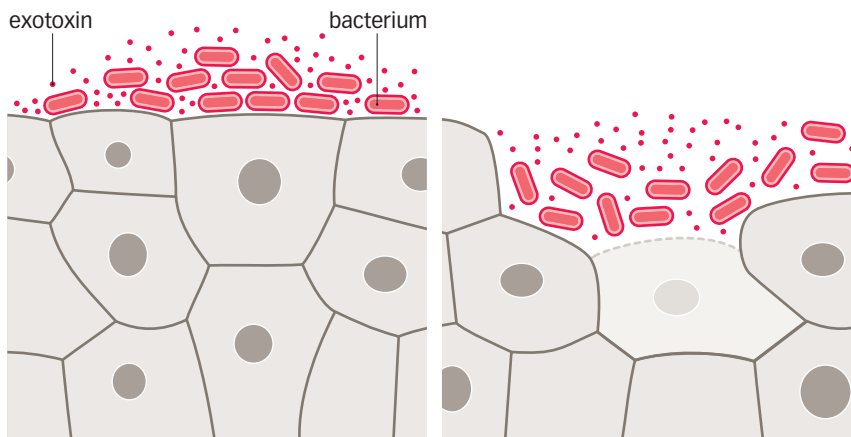
In the above discussions, we talked about some of the requirements for a successful infection. Now let's look at the damage that occurs to host cells during the disease process. Most of the damage associated with infection can be divided into two parts: damage that occurs because the bacteria are present, and damage that is a by-product of the host response. The damage directly attributable to the pathogen can be either direct or indirect.

*Direct damage* is the obvious destruction of host cells and tissues and is usually localized to the site of the infection. In direct damage, the host defense response is timely and potent, usually limiting the damage done. *Indirect damage* is seen in most serious infections and is much more dangerous to the host because it involves systemic disease. This type of distal pathology results from the production of bacterial toxins. These toxins (which can be very poisonous) are soluble in aqueous solutions and easily diffuse into, and move through, the blood and lymph systems. Thus, they can travel throughout the body quickly. This causes pathogenic changes far away from the initial site of infection.

Toxins can produce fatal outcomes in patients. They also have some common characteristics associated with them, such as fever, shock, diarrhea, cardiac and neurological trauma, and destruction of blood vessels. There are two types of toxin — exotoxins and endotoxins — and they are very different from each other.

### Exotoxins

**Exotoxins** are toxins that are produced by pathogens and then leave the pathogen cells and enter host cells (**Figure 5.16**). They are among the most lethal substances known, with some exotoxins a million times more poisonous than the poison strychnine. An exotoxin is usually an enzymatic protein that is soluble in blood and lymph. Being soluble in these liquids, exotoxins rapidly diffuse into tissues and stop metabolic function in the host cell. They are so dangerous that they are usually produced by pathogens in the *proenzyme* form, which is inactive, and then activated only after having left the pathogen's cells. Many of the genes that encode these toxins are carried on *plasmids* in the pathogens, which make them even more dangerous because the plasmids make it possible to transfer genetic information from one bacterium to another (discussed in Chapter 11).



**Figure 5.16 Exotoxins are produced by living pathogenic bacteria.** These toxins then enter cells of a host and prevent those cells from functioning properly.

There are three types of exotoxin: **cytotoxins**, which kill cells that they come in contact with; **neurotoxins**, which interfere with neurological signal transmission; and **enterotoxins**, which affect the lining of the digestive system (**Table 5.3**). Let's look at some of the more dangerous exotoxins.

Exotoxin	Organism Producing Toxin	Action of Toxin	Symptoms
Anthrax (cytotoxin)	<i>Bacillus anthracis</i>	Increases vascular permeability	Hemorrhage and pulmonary edema
Enterotoxin (enterotoxin)	<i>Bacillus cereus</i>	Causes host body to lose electrolytes	Diarrhea
Botulinum (neurotoxin)	<i>Clostridium botulinum</i>	Blocks release of acetylcholine	Respiratory paralysis
Alpha (gas gangrene); (cytotoxin)	<i>Clostridium perfringens</i>	Breaks down cell membranes	Extensive cell and tissue destruction
Tetanus (neurotoxin)	<i>Clostridium tetani</i>	Inhibits motor-neuron antagonists	Violent skeletal muscle spasms (lockjaw), respiratory failure
Diphtheria (cytotoxin)	<i>Corynebacterium diphtheriae</i>	Inhibits protein synthesis	Heart damage, possible death weeks after apparent recovery
<i>E. coli</i> (enterotoxin)	<i>Escherichia coli</i> O157:H7	Hemolytic uremic syndrome	Destruction of intestinal lining, kidney failure
Bacillary dysentery (enterotoxin)	<i>Shigella dysenteriae</i>	Poisons host cells	Severe diarrhea
Vibrio (enterotoxin)	<i>Vibrio cholerae</i>	Causes excessive loss of water and electrolytes	Severe diarrhea; death can occur within hours
Erythrogenic (cytotoxin)	<i>Streptococcus pyogenes</i>	Causes vasodilation	Maculopapular lesions, as seen in scarlet fever

Table 5.3 Effects of Exotoxins

### Anthrax Toxin

Anthrax toxin is a cytotoxin produced by the bacterium *B. anthracis*, a Gram-positive rod commonly found in the soil of pastures. The toxin is made up of three parts: an edema factor, a protective antigen, (which is a transmembrane factor also used for vaccine production); and a lethal factor. It is so dangerous that each bacterium produces the parts separately and assembles them on the bacterial cell surface in such a way that the complex is not yet toxic. The complex then leaves the bacterium and attaches to a host cell. Once attached to its target cell, the complex is endocytosed into a vesicle, where the low-pH environment causes a conformational change in the complex, converting it to the toxic form. In this state, the protective antigen forms a pore in the vesicle membrane, and the edema and lethal factors temporarily change their shape so that they can squeeze out into the host cell's cytoplasm.

Anthrax toxin interrupts the signaling capability of host macrophages and causes their death. It also interrupts the signaling capability of dendritic cells but does not kill them. However, even though they are still alive, the infected dendritic cells are no longer able to participate in the host defense against the infection. The importance of the loss of macrophage and dendritic cell function will become obvious in Chapters 15 and 16.

### Diphtheria Toxin

Diphtheria toxin is a cytotoxin that was discovered in the 1880s and is produced by the bacterium *Corynebacterium diphtheriae*. It works by inhibiting protein synthesis and is produced in an inactive form, just as anthrax toxin is. After secretion from the bacterium, the diphtheria toxin is changed enzymatically into an active form. This toxin is very potent, and a single molecule of it is sufficient to kill a cell.



#### Fast Fact

As with many other toxins, anthrax has become important in discussions of potential biological weaponry (Chapter 28).

The structure of the diphtheria toxin seems to be the same as that seen in many other exotoxins. It is composed of two polypeptide chains,  $\alpha$  and  $\beta$ . The  $\beta$  chain is responsible for binding to the target cell. This occurs through receptor molecules on the target cell and is followed by transport of the  $\alpha$  chain across the cell membrane. Once inside the host cell, the  $\alpha$  chain inhibits protein synthesis. Without the  $\beta$  chain, the toxin is harmless because it cannot gain entry into the host cell.

### Botulinum Toxin

Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*, a Gram-positive anaerobic rod. There are seven types of botulinum toxin, and all of them inhibit the release of the neurotransmitter acetylcholine. This disrupts the neurological signaling of skeletal muscles and results in paralysis. The mechanism of action is fascinating and uses specialized proteins known as *snare proteins* to block neurotransmitter release. These proteins are found on vesicle and cytoplasmic membranes in the host cell and normally facilitate the fusion of vesicles to the cell membrane so that routine exocytosis can occur. The botulinum toxin clips these snare proteins off the vesicle membranes, thereby disrupting fusion and inhibiting the exocytosis of the neurotransmitter. Because it affects muscles required for respiration, the resulting paralysis can lead to the death of the patient. Botulinum toxin has become a favorite candidate for potential use as a biological weapon (Chapter 28).

### Tetanus Toxin

Tetanus toxin is a neurotoxin produced by the bacterium *Clostridium tetani*, a Gram-positive, obligate, anaerobic rod commonly found in soil. This toxin is closely related to botulinum toxin and causes a loss of skeletal muscle control by blocking the relaxation impulse. This loss of control results in uncontrollable convulsive muscle contractions. The condition known as **lockjaw**, in which the facial muscles contract uncontrollably, is a symptom of infection with *C. tetani*.

### Vibrio Toxin



Vibrio toxin, also known as cholera toxin, is an enterotoxin produced by the bacterium *V. cholerae*. This toxin also consists of two polypeptide chains, with binding of the  $\beta$  chain to receptors on the target cell allowing the  $\alpha$  chain to enter the cell. Once inside, the  $\alpha$  chain induces the epithelial cells of the digestive system to release large quantities of electrolytes. The result is severe diarrhea and vomiting that can be lethal. One symptom of **cholera** seen in patients with advanced disease is what is called *rice-water stool*, in which the fecal material is mainly liquid with bits of mucus in it. Cholera is transmitted through the fecal-oral route of contamination and is an endemic problem in many parts of the world that are socioeconomically depressed. Treatment involves proper sanitation, killing of the organisms, and large-scale infusion of electrolyte solution.

### Other Exotoxins

Exotoxin effects are also seen in scarlet fever. Here, *S. pyogenes* produces a cytotoxin that destroys blood capillaries, and the result of this capillary destruction is the characteristic rash seen with this disease. If not treated, this exotoxin can cause occult heart damage that may lead to death.

The bacterium *Staphylococcus aureus* produces an enterotoxin that affects the digestive system and can cause **toxic shock**. This condition causes significant loss of liquids from the body, a loss that can lower the blood volume and blood pressure to the point at which the patient first goes into shock and then dies.

### Fast Fact

What would the cosmetic industry do without Botox® (a commercial brand of botulinum toxin) injections? No more wrinkles — because the muscles that would contract to form the wrinkles are actually paralyzed! But remember that the material they are injecting to get rid of those wrinkles is derived from one of the deadliest poisons ever known.

### Fast Fact

Staphylococcal organisms such as *S. aureus* can also cause a form of toxic shock that has been found to be associated with the use of tampons. The exact connection remains unclear, but researchers suspect that certain types of high-absorbency tampon provide a moist, warm environment where these organisms can thrive.

Fortunately, exotoxins are very *antigenic*, which means they are substances that stimulate a host to produce antibodies. It is therefore relatively easy to generate antibodies against these toxins. In fact, the DTaP vaccination that children receive is made up of the exotoxins from *C. diphtheriae* and *C. tetani* coupled with antigenic components of *Bordetella pertussis* (the organism that causes **whooping cough**). So that they can serve as vaccines, these toxins have been chemically treated to inactivate them. The treatment causes them to lose their toxicity but not their antigenicity (the ability to induce an antibody response). After this inactivation treatment, toxins are referred to as **toxoids**.

### Endotoxins

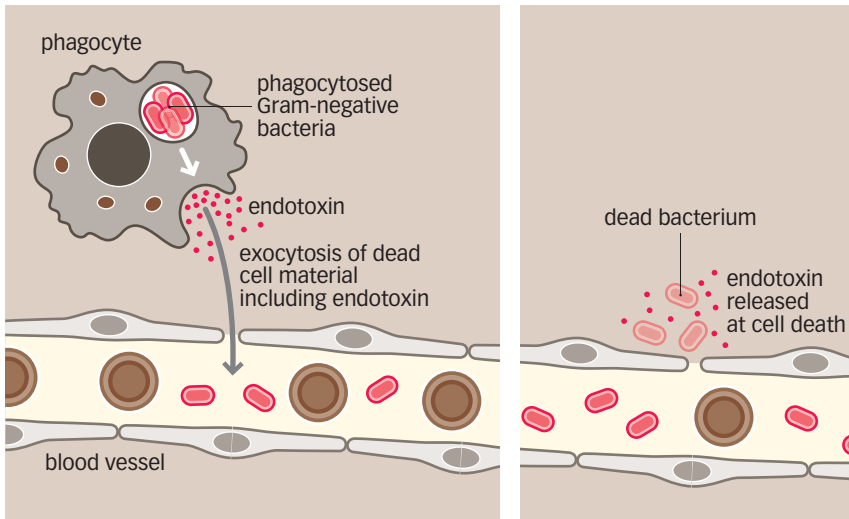
**Endotoxins** are bacterial toxins that are part of the cell wall of Gram-negative bacteria. They are active only after a bacterium containing them has been killed. Once the bacterial cell is dead, the endotoxins leave the cell wall and enter the bloodstream of the infected host.

Endotoxins are very different from exotoxins (**Table 5.4**). For a start, endotoxins are a component of Gram-negative organisms, whereas most exotoxins are produced by Gram-positive organisms. Endotoxins are not nearly as toxic and are part of the bacterial cell wall. We will see in Chapter 9 that Gram-negative bacteria have an outer layer made up of lipoproteins, phospholipids, and lipopolysaccharides. While the organism is alive, this outer layer stays in place around the cell, but when the organism dies, the layer falls apart (**Figure 5.17**). The lipopolysaccharides of this layer contain a particular lipid called lipid A, which has endotoxin properties.

All endotoxins cause essentially the same symptoms: chills, fever, muscle weakness, and aches. However, large amounts of endotoxin can cause more serious problems, such as shock and **disseminated intravascular clotting (DIC)**, a condition in which minor clotting occurs throughout the body. This minor clotting uses up the clotting elements so that they are not available when needed for serious blood loss situations.

**Table 5.4 A Comparison of Exotoxins and Endotoxins**

Property	Exotoxins	Endotoxins
Organism	Almost all Gram-positive	Almost all Gram-negative
Location	Extracellular, excreted by living organisms	Part of pathogen cell wall, released when cell dies
Chemistry	Polypeptide	Lipopolysaccharide complex
Stability	Unstable; denatured above 60°C	Stable; can withstand 60°C for hours
Toxicity	Among the most powerful toxins known (100 to 1 million times more lethal than strychnine)	Weak, but fatal at high doses
Effects	Highly specific, several types	Nonspecific; local reactions, such as fever, aches, and possible shock
Fever production	No	Yes, rapid rise to very high fever
Usefulness as antigen	Very good, long-lasting immunity conferred	Weak, no immunity conferred
Conversion to toxoid form	Yes, by chemical treatment	No
Lethal dose	Small	Large
Typical infections caused	Botulism, gas gangrene, tetanus, diphtheria, cholera, plague, scarlet fever, staphylococcal food poisoning	Salmonellosis, typhoid fever, tularemia, meningococcal meningitis, endotoxic shock



**Figure 5.17 A diagrammatic representation of endotoxin release.** Endotoxins are components of the Gram-negative cell wall, and on the death of the cell they are released to travel through the blood.

Endotoxins can sometimes elicit antibody production in the host, but in general this immune response is extremely weak because endotoxins are not very antigenic. As a result, the antibody response to them is usually poor. One of the problems with endotoxins is that because they are the result of cell death, they can contaminate materials and equipment used in clinics and hospitals, and remain toxic for long periods. This potential for long-term contamination makes the chance of endotoxins being transferred to patients a problem. Therefore, a test to determine whether there is endotoxin contamination of supplies or equipment was developed. This test is referred to as the ***Limulus* amebocyte lysate assay (LAL)** and takes advantage of the white blood cells of the horseshoe crab (*Limulus*), which are very different from human white blood cells. In the presence of endotoxin, *Limulus* white blood cells clot into a gel-like matrix that becomes turbid (cloudy). The degree of turbidity can be used as a measure of the amount of endotoxin contamination present.

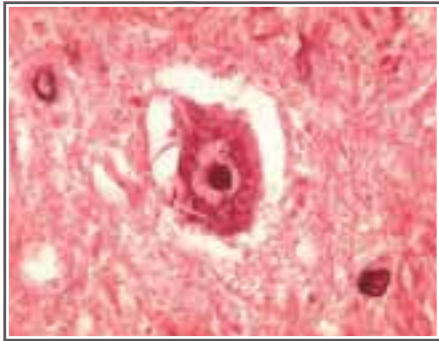
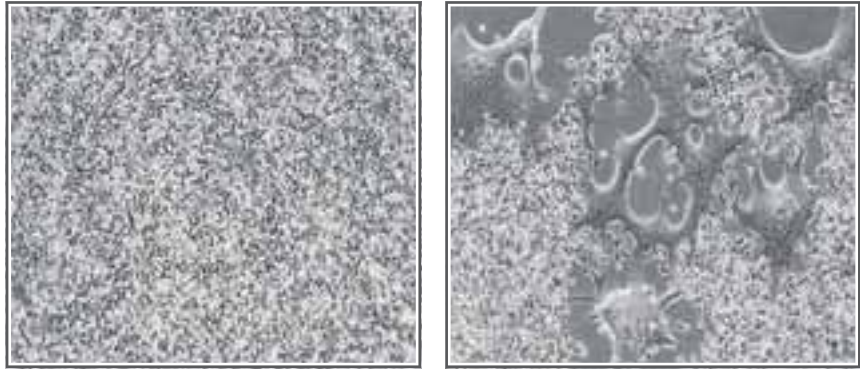


### Keep in Mind

- Damage to the host can be either direct or indirect. Direct damage is usually localized, and indirect damage is usually through the production of toxins.
- Exotoxins are extremely lethal substances produced by living cells (usually Gram-positive) and in most cases are proteins.
- Exotoxins can be cytotoxins (which kill cells), neurotoxins (which interfere with neurological signaling), or enterotoxins (which affect the lining of the digestive system).
- Exotoxins can cause the production of antibody.
- Endotoxins are contained inside the bacterial cell wall and are released on the death of the organism.
- Endotoxins are products of Gram-negative organisms, do not effectively cause the generation of antibody, and are less toxic than exotoxins.
- Lipid A, which is part of the Gram-negative phospholipid outer layer of the bacterial cell wall, has endotoxin properties.

**Figure 5.18** Cytopathic effects of viral infection caused by viral overload.

The left panel shows uninfected cells, which grow to confluence (meaning that they completely cover the surface). The right panel shows the same cells after viral infection. The host cells are destroyed as the viral particles burst out and enter the surrounding cells, causing their destruction.



**Figure 5.19** The cytopathology of the rabies virus, which produces large Negri bodies in the cell. These inclusion bodies contain newly formed viral particles.

**Viral Pathogenic Effects**

The pathogenic effects caused by viruses are discussed in detail in Chapters 12 and 13. For now, we can say that we classify virally caused cell damage or death as a **cytopathic effect (CPE)** and that the cytopathology associated with viral infections can occur in three ways.

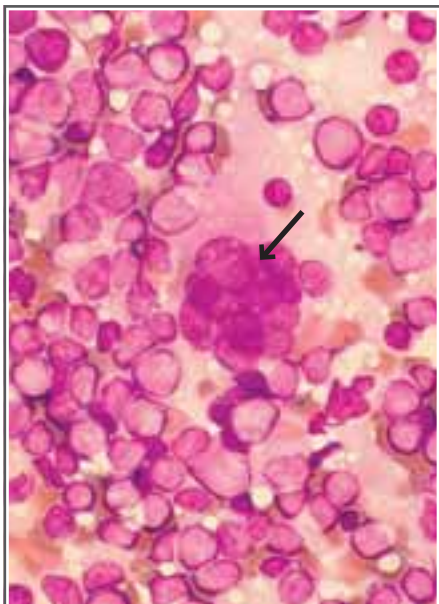
The most obvious way is *viral overload*, a condition that causes the virus to explode out of the host cell and infect and lyse surrounding host cells (**Figure 5.18**). A second type of CPE occurs when host defense mechanisms identify and kill virally infected cells. This is categorized as a **cytotoxic effect**. The third type of viral cytopathology occurs when a virus shuts down the host DNA, RNA, and protein synthesis and thereby forces the host cell to devote all its efforts to virus production. This is classified as a **non-cytotoxic effect**.

Viral cytopathology can be identified microscopically. In some cases, **inclusion bodies** filled with virus become visible inside the cell. For example, **Negri bodies** are inclusion bodies seen in rabies viral infections (**Figure 5.19**) and can be diagnostic for the disease. Some viral infections cause breaks in the host chromosomes, and these breaks are easily identifiable. The formation and appearance of *syncytia* (gigantic cells formed as a number of infected host cells merge; this is discussed in Chapter 13) can also be a visual indication of viral infection (**Figure 5.20**). More subtle pathogenic effects, such as the production of hormones or interferon, are also signs of virally infected cells.

The pathogenic effects seen in diseases caused by fungi and parasites will be discussed in Chapter 14.

**SUMMARY**

- The requirements for infection include entry, establishment, avoiding host defenses, damaging the host, and exiting from the host.
- Portals of entry for pathogens include skin, parenteral routes, and the mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts.
- Pathogens use virulence factors such as adhesins to establish themselves in the host.
- To avoid being killed by the host's defenses, pathogens use an array of virulence factors, including capsules, M proteins, mycolic acids, leukocidins,



**Figure 5.20** Formation of syncytia (arrow) in cells infected with virus. Formation of these structures is one type of cytopathic effect seen in viral infections.

hemolysin, coagulase, kinases, hyaluronidase, and collagenase.

- Some bacterial pathogens cause damage to host cells by releasing exotoxins; these include specific types such as cytotoxins, neurotoxins, and enterotoxins.
- Endotoxins on the cell wall of Gram-negative bacteria cause damage to the host and are released and disseminated when the bacterial cell dies.

Overall, the basis for our discussion here was the ability of pathogens to invade a host, remain in that host, and defend against host defenses so as to cause disease. As you organize and reflect on the concepts in this chapter, keep in mind what you have learned in the previous chapters. We explore the structures of the bacterial cell in Chapter 9, and there you will be able to reaffirm the connection with the disease processes you have learned here and those structural components.

## SELF EVALUATION AND CHAPTER CONFIDENCE

### Multiple Choice

Answers are given in the back of the book and help can be found in the student resources at:

[www.garlandscience.com/micro](http://www.garlandscience.com/micro)

- You nicked yourself while shaving and it has become infected. Which of the following portals of entry did the pathogen most probably use?
  - Gastrointestinal tract
  - Skin
  - Respiratory tract
  - Genitourinary tract
  - Exotoxin tract
- You overhear that the microbe causing an infection in your patient got into the body via the parenteral route. What does this actually mean?
  - It entered through the nervous system.
  - It entered and exited through the digestive system.
  - It entered through a break in the skin.
  - It entered by using cytotoxins.
  - It was inhaled through the respiratory system.
- A pathogen has entered the body. All of the following will have a role in its establishment except
  - Using fimbriae to attach to cell receptors
  - Releasing several exotoxins to destroy host cells
  - Using adhesins to attach to tissues
  - Creating a biofilm on a body surface
  - Releasing endotoxin that will cause clotting
- The  $LD_{50}$  of a pathogen is the number of organisms required to
  - Benefit 50% of the hosts
  - Infect 50% of the hosts
  - Kill 50% of the hosts
  - Produce lytic deaminase toxin
  - None of the above
- Imagine you are working in a lab and read reports about two different bacteria. Organism A has an  $ID_{50}$  of 20 cells, whereas organism B has an  $ID_{50}$  of 100 cells. Which of the following conclusions would you make?
  - Organism A must have endotoxin.
  - Organism A could be considered more virulent than organism B.
  - Organism B could be considered more virulent than organism A.
  - Organism B has a portal of entry but organism A does not.
- A bacterial toxin that causes damage to the plasma membrane of host red blood cells which results in lysis is
  - Coagulase
  - Leukocidin
  - Hyaluronidase
  - Collagenase
  - Hemolysin
- A bacterial enzyme that breaks down connective tissue is
  - Coagulase
  - Hemolysin
  - Hyaluronidase
  - All of the above
  - None of the above
- An invasin would be used by a microbe to
  - Change the nuclear structure of host cells
  - Inhibit the functions of host ribosomes
  - Increase the rate of bacterial division
  - Change the structure of actin filaments in host cells
  - Change the shape of microtubules in host cells

9. You are working in a clinical lab and have a culture of cells that are producing exotoxins. On the basis of this information, the organisms are most probably
- Gram-negative bacteria
  - Viruses
  - Gram-positive bacteria
  - All dead
  - None of the above
10. Three types of exotoxin are
- Febrile toxins, enterotoxins, and neurotoxins
  - Neurotoxins, cytotoxins, and febrile toxins
  - Cytotoxins, diarrhea toxins, and neurotoxins
  - Neurotoxins, cytotoxins, and enterotoxins
  - None of the above combinations
11. Botulism toxin is
- A neurotoxin
  - A muscular toxin
  - A febrile toxin
  - An enterotoxin
  - None of the above
12. Many people refer to tetanus infection with the pathogen *Clostridium tetani* as lockjaw. Which of the following best explains why?
- These bacteria produce a capsule that hardens the surface of the jaw.
  - These bacteria produce a toxin that causes jaw muscles to remain contracted.
  - These bacteria accumulate in the jaw and prevent proper jaw movement.
  - These bacteria produce an enzyme that breaks apart jaw muscle cells.
13. Which of the following would best describe endotoxins?
- They are toxins found on Gram-negative cell walls.
  - They are toxins that are released by Gram-positive cells.
  - They are toxins that are produced by dead Gram-positive and Gram-negative cells.
  - They are toxins found on Gram-positive cell walls.
  - They are identical in structure to exotoxins.
14. You are caring for a new patient in the intensive care unit and see in his chart that he has disseminated intravascular clotting (DIC). On the basis of the information you learned in this chapter, the patient's disease is caused by
- Exotoxins
  - Enterotoxins
  - Endotoxins
  - Vascular toxins
  - Neurotoxins

## DEPTH OF UNDERSTANDING

Questions listed here require you to bring together the concepts you have learned in this chapter into a discussion format. This helps you to increase your depth of understanding of the material you have learned. Help can be found in the student resources at: [www.garlandscience.com/micro](http://www.garlandscience.com/micro)

- Compare the portals of entry used by bacteria and give examples of organisms that use each portal.
- Discuss the mechanisms that bacteria use to avoid or defeat the host defenses.
- Describe the properties of exotoxins and compare them with endotoxins.

## CLINICAL CORNER

Help can be found in the student resources at: [www.garlandscience.com/micro](http://www.garlandscience.com/micro)

- Neisseria meningitidis*, commonly known as meningococcus, is a Gram-negative bacterium that not only can cause meningitis but can also enter the bloodstream and cause a deadly infection of the blood. If the bacteria do invade the bloodstream, the death rate can be very high. Luckily, if it is detected early, doctors can administer antibiotics that kill the bacteria. However, once antibiotics have been administered and the bacteria are killed, the patient can often get much sicker before recovering.
  - Can you identify the virulence factor that might be responsible for this “turn for the worse” after antibiotic killing of these Gram-negative bacteria?
  - Imagine you must explain to the patient's concerned family what is happening inside the patient's body after antibiotic treatment. What would you say, in simple terms?
- Imagine a new drug has been designed that targets and destroys the M protein of a deadly strain of *Streptococcus*. It is experimental and your very ill patient might be able to benefit from this new treatment. The doctor has presented the idea to the patient's family but needs a signed consent. The family is confused, however, about how this treatment will actually work. They've never heard of something called M protein. They turn to you to see whether you know how this might help. How would you explain this to them in simple terms they can understand? (Be sure to explain to them what you know about M protein, what it does, and what the benefits of destroying it would be.)