bile detergents can destroy organisms with envelopes, such as certain viruses. As in the skin, antimicrobial *defensins* are produce by gut epithelial cells. *IgA antibodies*, produced in mucosal lymphoid tissues such as Peyer patches and secreted into the gut lumen (Chapter 18), can neutralize potential pathogens. *Peristalsis* can clear organisms, preventing their local overgrowth. Finally, as already mentioned, the *normal gut flora* creates a microenvironment that discourages colonization by potential pathogens, such as *Clostridium difficile*.

Gastrointestinal tract infections may occur when local defenses are circumvented by a pathogen, or when they are so weakened that even normal flora produce disease. Many notorious gastrointestinal pathogens are intrinsically resistant to local defenses, particularly those that enter the host by ingestion. *Norovirus* (the scourge of the cruise ship industry) is a non-enveloped virus that is resistant to inactivation by acid, bile, and pancreatic enzymes and hence easily spread in places where people are crowded together. Similarly, intestinal protozoa and some intestinal helminths transmitted as cysts or eggs, respectively, have acid-resistant outer coats, and some bacteria, such as *Shigella*, are also resistant to acid; hence, as few as 100 organisms of each can cause illness.

Enteropathogenic pathogens may establish symptomatic gastrointestinal disease through several distinct mechanisms:

- *Adhesion and local proliferation.* Examples include *V. cholerae* and enterotoxigenic *Escherichia coli*, which bind to the intestinal epithelium and multiply in the overlying mucous layer. Here, these organisms elaborate potent exotoxins that are responsible for symptomatic disease.
- *Adhesion and mucosal invasion.* Pathogens such as *Shigella*, *Salmonella enterica*, *Campylobacter jejuni*, and *Entamoeba histolytica* invade the intestinal mucosa and lamina propria and cause ulceration, inflammation, and hemorrhage that manifest clinically as dysentery.
- *"Hijacking" of host pathways of antigen uptake.* You will recall that mucosal lymphoid tissues such as Peyer patches are covered by specialized epithelial cells called M cells, which are responsible for uptake and delivery of antigens to underlying lymphoid tissues. Ironically, multiple infectious agents, including poliovirus, are taken up into the host through this same pathway.

There are several caveats to the themes laid out above. Some organisms contaminating food can produce gastrointestinal disease without ever establishing an infection in the host. A cardinal example is *S. aureus*, which elaborates a powerful exotoxin during its growth in contaminated food that is responsible for acute food poisoning. Diminished local defenses due to loss of gastric acidity, broad-spectrum antibiotic treatment, ileus, or mechanical obstruction may exacerbate infections caused by virulent pathogens and allow organisms of low pathogenecity to establish disease. Other opportunistic organisms such as *Candida* only produce gastrointestinal disease when the immune system is weakened. In this setting, *Candida* has a particular predilection for establishing infections in squamous mucosae (e.g., oral thrush, esophagitis), but may also involve other sites.

Respiratory Tract

A plethora of microorganisms, including viruses, bacteria, and fungi, are inhaled daily, mainly in dust or aerosol particles. The distance these particles travel into the respiratory system is inversely proportional to their size. Large particles are trapped in the mucociliary blanket that lines the nose and the upper respiratory tract. Microorganisms trapped in the mucus layer are transported by ciliary action to the back of the throat, where they are swallowed and cleared. By contrast, particles smaller than 5 microns are carried into the alveoli, where they are phagocytosed by resident alveolar macrophages or by neutrophils recruited to the lung by cytokines.

The microorganisms that infect the healthy respiratory tract evade local defenses through several different mechanisms. Some pathogenic respiratory viruses attach to and enter epithelial cells in the lower respiratory tract and pharynx. For example, influenza viruses have envelope proteins called hemagglutinins that bind to sialic acid on the surface of epithelial cells. Attachment induces the host cell to endocytose the virus, leading to viral entry and replication. The resulting damage to the respiratory epithelium sets the stage for superinfection by *S. pneumoniae* and *S. aureus*, often leading to serious pneumonias. Certain bacterial respiratory pathogens, including *Haemophilus influenzae*, *M. pneumoniae,* and *Bordetella pertussis*, release toxins that enhance their ability to establish an infection by impairing ciliary activity. Another important mechanism of establishing respiratory infection is primary resistance to killing following phagocytosis. A classic example is *Mycobacterium tuberculosis*, which gains a foothold in alveoli by surviving within the phagolysosomes of macrophages.

Other organisms establish disease when local or systemic defenses are impaired. Chronic impairment of mucociliary defense mechanisms occurs in smokers and in people with cystic fibrosis, while acute injury occurs in patients undergoing mechanical ventilation and in those who aspirate gastric acid. Many other infectious agents cause respiratory infections primarily in the setting of systemic immunodeficiency. Examples include fungal infections by *P. jiroveci* in AIDS patients and by *Aspergillus* species in patients with neutropenia.

Urogenital Tract

Urine is sterile, and the urinary tract is protected from infection by regular emptying during micturition. Urinary tract pathogens (e.g., *E. coli*) almost always gain access via the urethra and must be able to adhere to urothelium to avoid being washed away. Anatomy plays an important role in dictating risk. Women have more than 10 times as many urinary tract infections as men because the distance between the urinary bladder and skin (i.e., the length of the urethra) is 5 cm in women versus 20 cm in men. Understandably, **obstruction of urinary flow or reflux of urine compromises normal defenses and increases susceptibility to urinary tract infections**.

From puberty until menopause the vagina is protected from pathogens by lactobacilli, which ferment glucose to lactic acid, producing a low pH environment that suppresses the growth of pathogens. Antibiotics can kill the lactobacilli and allow overgrowth of yeast, causing vaginal