parenchyma play an essential role in initial clearance and killing of pathogens.

Gastrointestinal defenses include gastric acidity, which kills many organisms, and vomiting and diarrhea, which help to clear pathogens from the gut. Bacteria vary greatly in their susceptibility to gastrointestinal host defenses. For example, as few as 10 *Shigella* organisms can cause infection, whereas 10^5 to 10^8 *Vibrio cholera* organisms are required for infection.

The urinary tract is protected physically by regular urine flow, the acidity of the urine, and antibacterial proteins. Conditions that interfere with these factors (e.g., prostatic hypertrophy, renal stones) may lead to stasis and infection. Mechanical injection of bacteria through the urethra into the bladder, as occurs in women during sexual intercourse, can lead to colonization of the bladder and infection. Injuries or devices that damage or bypass anatomic barriers frequently lead to infection. Examples include burns, intravenous catheters, intubation, urinary tract catheters, surgery, and trauma.

The normal microbiologic flora on the skin and in the respiratory and gastrointestinal tracks is an important component of host defenses. Normal florae compete with pathogens for nutrients and have antimicrobial activity of their own. Disruption of the normal flora by antibiotics allows superinfecting organisms such as *Candida* species and *Clostridium difficile* in the gut to colonize and then cause infection.

Organs that clear organisms from the bloodstream and lymph, including the liver, spleen, and lymph nodes, play an essential role after a pathogen has breached the primary anatomic barriers. Lack of a spleen increases a person's susceptibility to overwhelming sepsis caused by encapsulated bacteria including *S. pneumoniae, Neisseria meningitidis,* and *H. influenzae.* Cirrhosis of the liver allows portal vein blood to bypass the liver, increasing susceptibility to infection by gut flora.

Innate Immunity

Innate immunity refers to cells, molecules, and cellular receptors that recognize pathogens and promote inflammation nonspecifically at the site of infection. Table 86-1 compares innate and adaptive immunity. The response of innate immunity is relatively nonspecific, invariant, rapid, and without memory. Adaptive immunity is highly specific, slow during primary infection, and can be recalled after primary infection with a more rapid, robust response.

TABLE 86-1 FEATURES OF THE INNATE AND ADAPTIVE IMMUNE RESPONSES

INNATE RESPONSE	ADAPTIVE RESPONSE
No memory: quality and intensity of response invariant	Memory: response adapts with each exposure
Recognizes limited number of nonvarying, generic molecular patterns on or made by pathogens	Recognizes vast array of specific antigens* on or made by pathogens
Pattern recognition mediated by a limited array of receptors	Antigen recognition mediated by a vast array of antigen-specific receptors
Response immediate on first encounter	Response on first encounter takes 1-2 weeks; on second encounter, 3-7 days

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*Antigen is a molecular structure (e.g., protein, peptide, lipid, carbohydrate) that generates an immune response.

The molecules involved in innate and acquired immunity include cytokines, chemokines, and integrins. Cytokines are soluble proteins that have numerous functions, including promoting cellular growth and activation as well as regulating the adaptive immune response (Table 86-2). Their functions range from stimulating the production of and activating inflammatory cells, including neutrophils, macrophages, and eosinophils, to the direct antiviral action of interferons. Some activate endothelial cells and cause fever, whereas others are regulatory and downregulate the inflammatory response.

Concentration gradients of chemokines in tissue attract leukocytes to areas of inflammation. Integrins on the surface of leukocytes allow adhesion to receptors on other types of cells such as vascular endothelium. This is the first step in attracting and localizing leukocytes to areas of inflammation.

Relatively nonspecific pathogen recognition receptors on phagocytes include toll-like receptors (TLRs), which were originally described in the fruit fly, *Drosophila*; oligomerization domain–like receptors (often abbreviated as Nod-like receptors); C-type lectin-like receptors; and intracellular receptors that detect double-stranded RNA. TLRs have been studied extensively (Table 86-3). TLRs are located on several cell types, including macrophages and dendritic cells. When a pathogen is detected by its adherence to a TLR on the surface of a cell, activation of nuclear transcription factors, including nuclear factor-κB, occurs. This stimulates the production of numerous cytokines important in the inflammatory response, including interleukin-1 (IL-1), IL-6, IL-10, IL-15, TNF-α, and growth factors (see Table 86-2). These cytokines amplify the inflammatory response by activating effector cells and by stimulating the production of many other inflammatory factors, including IL-2, interferons, C-reactive protein, complement components, and growth factors.

Complement factors are soluble proteins and enzymes that are produced in the liver. Complement activation occurs through several pathways that are involved in the innate and acquired host defense system as shown in Figure 86-1. Complement activation can occur as a result of antigen-antibody immune complex binding of C1, the mannose-binding lectin pathway, or the alternative pathway, which can be activated by bacterial cell wall components.

The complement cascade results in C3 convertase, a protein that cleaves C3. Cleavage of C3 leads to the production of multiple proteins (C3a, C4a, and C5a) that stimulate histamine release from mast cells leading to vasodilatation, increased endothelial permeability, and attraction of activated neutrophils. A second cleavage product of C3, C3b, in conjunction with immunoglobulin G (IgG) stimulates phagocytosis of pathogens. Activation of C5-9 results in bacterial lysis. Patients deficient in the complement components C5-9 appear to be particularly susceptible to organisms such as *N. meningitides and Neisseria gonorrhoeae.* Complement activation is regulated by several regulatory proteins, such as C1 esterase inhibitor that inhibits the inappropriate activation of the classic complement activation pathway.

The inflammatory response results in the clinical signs of inflammation, including erythema, tenderness, warmth, and swelling. It can be initiated by microorganisms in tissue, tissue